Progress against non-Hodgkin lymphoma in the Netherlands: Incidence, patterns of care and prognosis since 1989

Studies with cancer registry data

Vooruitgang bij het non-Hodgkin lymfoom in Nederland: Incidentie, zorggebruik en prognose sinds 1989

Studies met kankerregistratie data

Saskia van de Schans

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Contents

Chapter 1

General introduction

Introduction

Haematopoietic and lymphoid tissue malignancies

Cancers arising from the haematopoietic and lymphoid tissue comprise a heterogeneous group of malignancies with diverse clinical and biological features. The World Health Organization (WHO) classification of Haematopoietic and Lymphoid tissue,[1] classified these cancers based on histologic characteristics. Lymphoid neoplasms are divided into precursor, mature indolent B-cell, mature aggressive B-cell, mature T- and NK-cell, plasma cell, and Hodgkin lymphoma. Myeloid neoplasms are divided into myeloproliferative, myelodysplastic, myeloproliferative/myelodysplastic neoplasms, acute myeloid leukaemia, and other acute leukaemias. Furthermore, a group of histiocytic and dendritic cell neoplasms is specified. All mature B-cell neoplasms (minus plasma cell neoplasm) and all T- and NK-cell neoplasms together are called non-Hodgkin lymphomas (NHL).

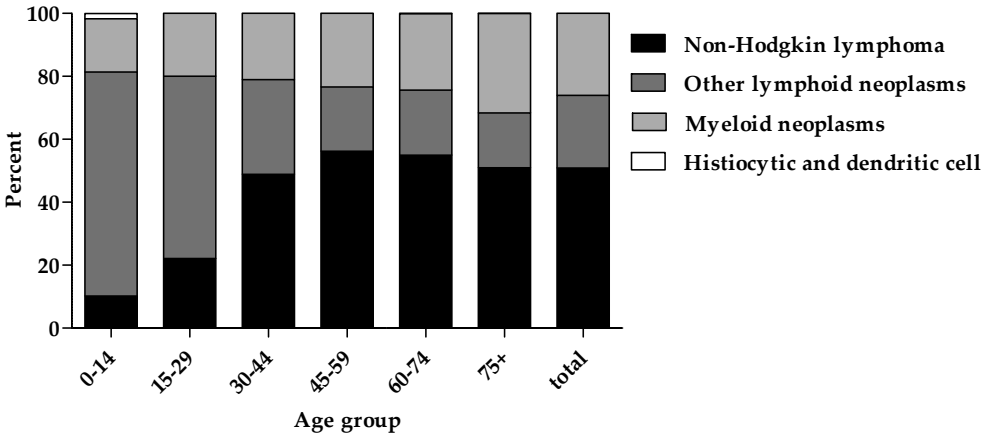

Figure 1: Major subgroups of haematopoietic and lymphoid neoplasms by age group.

These large groups are subdivided into several entities according to clinical presentation, morphology, immunophenotype, and genetic criteria. The various NHL entities are described in table 1 of chapter 2.1 and are used in most studies in this thesis. For chapter 1.2 this was not possible because specific morphology codes were not available in the EUNICE database. EUNICE is a combination of eleven dedicated cancer registries across Europe. Therefore we used the WHO International Classification of Diseases (ICD10) that classifies NHL as C82-C85.[2] With this classification Waldenström macroglobulinaemia, chronic lymphocytic

leukaemia, prolymphocytic leukaemia, heavy chain disease and hairy-cell leukaemia are excluded from NHL.

Incidence and mortality

Haematopoietic and lymphoid tissue malignancies represent around 7% of all new malignancies and deaths of malignancies in Europe.[3] In the Netherlands 6,908 patients with haematopoietic and lymphoid neoplasms were diagnosed in 2007, of whom 1,706 indolent B-cell, 1,566 aggressive B-cell, and 254 T- and NK-cell neoplasms. In 2007, 3,084 patients died of haematopoietic and lymphoid cancers out of an estimated prevalence of 17,000 NHL patients.[4] The incidence and mortality rates are usually 30% higher in males than females.[5] Haematopoietic and lymphoid cancers clearly occur rather frequently in the elderly the incidence being 5 times higher in people aged 75 and older and 3 times higher in people aged 60-74, compared to 45-59 year old people.[4] Incidence and mortality in the Netherlands are in range with other European countries.[3] NHL is the most common haematopoietic and lymphoid tissue neoplasm in adults in almost all populations worldwide.[6] Over the last decades, the incidence of NHL has been rising in Europe and North America.[7,8] Mortality rose until the mid 1990s, and started to level off or even decline in the following decade.[7] Some risk factors have been identified for NHL subtypes: immunodeficiency disorders, immunesuppression, infectious agents, autoimmune disorders and a positive family history of haemato-lymphoproliferative malignancies.[9,10] Other factors such as exposure to chemicals, ultra violet exposure, dietary and lifestyle factors and blood transfusions might also be related to lymphoma development.[11]

Stage

Clinical stage of most NHL entities is defined according to the Ann Arbor classification.[12] Stage I represents involvement of a single lymph node region or lymphoid structure. When two or more lymph node regions on the same side of the diaphragm are involved this is called stage II. Stage III has involvement of lymph node regions or structures on both sides of the diaphragm. When extranodal sites and nodal sites are involved stage IV is recorded.

Treatment options

For patients with indolent B-cell NHL several treatment options are available, dependent on the treatment goals of the individual patient. When quality-of-life is

the most important goal, wait and see policy or non-aggressive chemotherapy is the best option. For patients striving to long disease-free survival or prolonging survival aggressive chemotherapy or even stem cell transplantation are the options. For aggressive B-cell NHL treatment is dependent on stage. Stage I disease is nowadays treated with a combination of chemotherapy and radiotherapy.[13-15] For patients with advanced stage aggressive NHL chemotherapy alone is the first choice of treatment.[16] Since 2001 this chemotherapy is combined with anti-CD20 monoclonal antibodies (mostly rituximab).[17] Due to low prevalence of T- and NK-cell neoplasms, only few studies on treatment have been performed. Chemotherapy is still the most common treatment for this group.[18]

Survival

Survival is dependent on the NHL histological subtype with 5-year relative survival rates for indolent B-cell of 77%, for aggressive B-cell of 51%, and for T- and NK-cell of 42%.[4] Survival has been improving, but differences between geographical areas exist.[19-21] Survival is influenced by several factors: tumour related factors (low Ann Arbor stage, no bone marrow involvement, no splenic involvement, low number of nodal areas involved, low number of extranodal sites involved, low tumour size), patient related factors (female sex, being younger, high performance status, no co-morbidities) and other factors (no B-symptoms, no anaemia, no lymphocytopenia, no thrombocytopenia, normal serum lactate dehydrogenase levels, normal haemoglobin levels) all result in better survival.[22-27] These prognostic factors could be grouped into a prognostic index, which can predict the outcome of patients. Prognostic indices are different per NHL entity, e.g. IPI for aggressive B-cell neoplasms, FLIPI for follicular lymphoma and MIPI for mantle cell lymphoma.

Cancer registry data

Information on treatment and prognosis of NHL patients is mostly gathered in clinical trials. This is a good method for evaluating treatment options, in these selected patient groups, but might not be valid for everyday practice, where patients are older and have co-morbidity. In contrast, information of cancer registries can give insight into treatment and outcome for unselected patients.

Patients and methods

Cancer Registries

The Eindhoven Cancer Registry (ECR) was started in 1955 as part of a programme for nation-wide cancer registration. Data on all new cancer patients were collected directly from pathology reports and patients medical records. The registry was started in three hospitals in Eindhoven and gradually expanded to include the southeastern part of the province of North Brabant, the northern part of the province of Limburg (since 1970) and the middle and southwestern part of North Brabant since 1986 (except the small most western part) (figure 2). Other regional registries had discontinued their activities, until a successful nationwide program was re-established since 1984. Since 1989 the whole Dutch population was covered by nine regional cancer registries, which established the National Cancer Registry. In 2008, two comprehensive cancer centres (IKN and IKST) hosting two regional cancer registries have merged. The EUNICE database contains data from 12 European population-based cancer registries (including ECR). The project, data preparation, and inclusion criteria for survival analysis were described in detail before.[28] Furthermore, data from the study by Pulte et al.,[20] which were derived using the 1973-2004 limited-use database of the Surveillance, Epidemiology and End Results (SEER) Program, were used.

Eindhoven Cancer Registry

The area in the population-based Eindhoven Cancer Registry now hosts 2.4 million inhabitants, 10 general hospitals at 16 locations and served by 6 regional pathology laboratories, two large radiotherapy institutes and one neurosurgical centre.[29] The cancer registry is based on notification of all newly diagnosed malignancies by the automated pathology archive (PALGA). Additional sources are the national registry of hospital discharge, haematology departments and radiotherapy institutes. Completeness is estimated to be at least 95%.[30] Treatment decisions were generally made in multi-disciplinary meetings, within the framework of the comprehensive cancer centre. The region is characterized by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres. The population in the area is markedly aging due to longer life expectancy and a decreasing amount of births. This results in an increased proportion of elderly people.

Figure 2. The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre South

Trained registration clerks actively collect data on diagnosis, topography, histology, stage and information about initial treatment (delivered within 6 months from diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status.[31]

Co-morbidity

Since 1993, the Eindhoven Cancer Registry is the only cancer registry in the Netherlands that also registers the presence of serious co-morbidity with prognostic impact at the time of cancer diagnosis for all newly diagnosed patients. Co-morbidity was defined as any other disease that was present at the time of cancer diagnosis. Co-morbid conditions were registered as dichotomous variables (yes/no), according to the medical history of the patient, the use of relevant drugs and diagnostic work-up. In short, the following important conditions were recorded: chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), diabetes mellitus, hypertension, connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis, and other chronic infections (table 2).

Table 2: Co-morbid conditions registered by the Eindhoven Cancer Registry

Chronic obstructive pulmonary disease (COPD)
Cardiovascular disease: myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft (CABG)
Peripheral arterial disease: intermittent claudication, abdominal aneurysm, surgical intervention
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell carcinoma)
Hypertension
Diabetes mellitus
Other: - Autoimmune diseases: sarcoidosis, Wegener's disease, systemic lupus erythematosis (SLE) - Rheumatoid arthritis - Kidney diseases: glomerulonephritis, pyelonethritis - Gastrointestinal: stomach ulcer and resection, colitis - Liver diseases: cirrhosis, hepatitis - Dementia - Chronic infections

Mortality data

Data on mortality from NHL are not available in the Netherlands Cancer Registry and were derived from Statistics Netherlands (CBS).

Data analyses

Incidence and mortality

Because the age-distribution varies over time, and to enable international comparisons, age-adjustment was performed by direct standardization according to the European Standard Population (European Standardized Rates, ESR). Trends in incidence and mortality were estimated by calculating the estimated annual percentages change (EAPC). This was done by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable, i.e., $y=mx+b$ where $y=\ln(\text{rate})$ and $x=$calendar year. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.

Survival

Information on the vital status of all patients was obtained initially from the municipal registries and since 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all deceased citizens. Crude survival analyses were performed to evaluate the prognostic effects of treatment

and co-morbidity. Cox regression models were used to compute multivariable rates. Traditional cohort-based relative survival (the ratio of the observed to the expected rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival in a background population with the same sex and age structure.[32] To derive more up-to-date relative survival we used the period-based relative survival.[33] Expected survival rates were calculated from life tables for regional populations with the same 5-year age distribution.[34] Generalized linear models with a Poisson structure were used, based on collapsed data and exact survival times.[35]

Outline

The main objectives of the studies described in this thesis were:

1 Giving insight into the progress against NHL by studying the trends in incidence, treatment, and relative survival of non-Hodgkin lymphoma in a large population-based setting.
2 To investigate the relation between co-morbidity in newly diagnosed patients with non-Hodgkin lymphoma to explore possible aetiological factors.
3 To investigate determinants of survival on NHL, and validate prognostic indexes in unselected patients.
4 To explore variation among elderly with aggressive B-cell NHL with respect to patient characteristics for giving insight into adherence to guidelines for elderly patients. Furthermore explore the association between age, co-morbidity and performance status with treatment, treatment outcome and survival for selecting elderly subgroups of patients for whom treatment should be adapted.

Long-term trends in incidence, treatment, mortality, and survival of NHL patients are described in **chapter 2.1**. In **chapter 2.2** differences between relative survival trends within Europe and a comparison with relative survival in the US are presented. The relation between autoimmune and chronic inflammatory disorders on the one hand and lymphoid cancers on the other hand is covered in **chapter 3.1**. Validation, revision and extension of the follicular lymphoma international prognostic index (FLIPI) are depicted in **chapter 4.1**. **Chapter 4.2** describes the validation of the mantle cell lymphoma international prognostic index (MIPI).An overall overview of treatment and survival of elderly NHL patients in the Netherlands is shown

in **chapter 5.1**. An in-depth study concerning treatment and treatment outcome of these elderly patients is displayed in **chapter 5.2**. In **chapter 5.3** the association of diabetes mellitus on treatment and outcome of NHL is described. The general discussion (**chapter 6**) discusses the main results and perspectives for research and clinical management.

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Chapter 2

Long-term trends

2.1

Diverging trends in incidence and mortality, and improved survival of non-Hodgkin lymphoma, in the Netherlands, 1989-2007

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Submitted

Abstract

Background

We studied progress against non-Hodgkin lymphoma (NHL) in the Netherlands by describing the changes in incidence, treatment, relative survival and mortality by sex, during 1989 to 2007.

Patients and Methods

We included all adult patients with non-Hodgkin lymphoma (i.e. all mature B-, T- and NK-cell neoplasms, with the exception of plasma cell neoplasms), newly diagnosed during 1989-2007 and recorded in the 8 regional cancer registries of the Netherlands Cancer Registry (n=55,069). Regular mortality data were derived from Statistics Netherlands. Follow-up was completed up to January 1st, 2009. Three diagnostic groups were recognized: indolent B-cell (including CLL) (N=25,911), aggressive B-cell (N=25,341), and T- and NK-cell neoplasms (N=3,817). Annual percentage of change in incidence, mortality and relative survival were calculated.

Results

The incidence of indolent B-cell neoplasms and T- and NK-cell neoplasms rose significantly (EAPC 1.2% and 1.3%); incidence of aggressive B-cell neoplasms remained stable. Mortality due to NHL remained stable between 1989 and 2003, and decreased since 2003. The proportion of patients receiving chemotherapy and radiotherapy did not change significantly, detailed regimen changes being unrecorded, in our study period. Five-year relative survival rates for indolent B-cell neoplasms rose from 67 to 75%, and for aggressive B-cell neoplasms from 43 to 52%, but 5-year survival remained stable at 48% for T- and NK-cell neoplasms.

Conclusions

In the Netherlands, incidence of indolent B-cell and T- and NK-cell neoplasms increased since 1989, but remained stable for aggressive neoplasms. Survival increased for all mature B-cell neoplasms, preceding a declining mortality and increased prevalence of NHL (17,597 at January 1st, 2008).

Introduction

Cancers arising from lymphoid tissue are a heterogeneous group of malignancies, with varied clinical and biological features. According to the World Health Organization (WHO) classification of Haematopoietic and Lymphoid tissue, 4th edition,[1] these lymphoid cancers are divided into precursor, mature B-cell, and mature T- and NK-cell neoplasms. Based on histopathology, immunophenotype and genetic criteria these main diagnostic groups are subdivided into a large variety of separate entities (for the entities of non-Hodgkin lymphoma (NHL), see table 1). NHL is the most common haematologic malignant neoplasm in adults in almost all populations worldwide.[2] Over the last decades, the incidence of NHL increased in Europe and North America.[3,4] Mortality rose until the mid 1990s, and started to decline in the following decade.[3] While survival has been improving, substantial differences between geographical areas remain.[5-8]

For aggressive B-cell neoplasms, few options for improving diagnosis or for early detection exist; therefore improvement in survival is likely due to the application of better treatment strategies. From 1997, clinical studies, among others in the Netherlands, have shown that combining rituximab (an anti-CD20 monoclonal antibody) to standard chemotherapy regimens (cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP))[9,10] results in a major clinical benefit (increased response rate, and improved progression free and overall survival) in almost all subtypes of aggressive B-cell neoplasm, without relevant increase in toxicity.[11-17] The same is true for increased response rate, progression free survival, and most probably also for overall survival in many subtypes of indolent B-cell NHL.[12,18-21] For chronic lymphocytic leukemia (CLL) advances in diagnostic techniques, like flow cytometric methods, could also have led to better and earlier detection. Improvement of treatment outcome for patients with T- and NK-cell neoplasms was less impressive, with few novel agents.[22]

In this era of new, effective and expensive therapies insight into recent and long-term trends in incidence, treatment, survival and mortality in unselected patients serves to show real improvements, if any, and helps to anticipate to consequences and future developments.

Methods

Study population and data collection

Population-based data were obtained from the 8 regional registries maintained and hosted by the Comprehensive Cancer Centers that constitute the nationwide Netherlands Cancer Registry (NCR), which started in 1989.[23] The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated national pathology archive to which all pathology laboratories subscribe (PALGA). Additional sources are the national registry of hospital discharge, various haematology and clinical chemistry departments and radiotherapy institutions. Trained registrars routinely collect data on patient and tumour characteristics such as date of diagnosis, tumour grade, Ann Arbor stage, and primary treatment. Morphology, topography, and cell lineage (e.g. B-cell, T-cell, NK-cell) are coded according to the International Classification of Diseases for Oncology (the 2nd edition until 2000 and 3rd edition as of 2001).[24] The quality of the data is high, due to thorough and uniform training of the registration clerks and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%,[25] except for chronic lymphocytic leukemia, a diagnosis regularly made without tissue specimens.[26] Follow-up of vital status of all patients was calculated as time from diagnosis to death or to January 1st, 2009. If patients were lost to follow-up the last date of contact was used for censoring. The information on vital status was initially obtained from municipal registries and since 1995 from the nationwide population registries network (GBA) that provides virtually complete coverage of all deceased Dutch residents, including possible dates of emigration (<0.6%) which then became the date of censoring.

For the present study, all newly diagnosed patients with mature B-, T- and NK-cell neoplasms during 1989-2007 in the Netherlands were selected. Due to its specific clinicopathological characteristics plasma cell neoplasms were excluded, leaving 55,069 cases of non-Hodgkin lymphoma. Since many entities are rare diseases, we used three major diagnostic groups, based on a combination of entities of more or less similar clinical behavior and similar response to (novel) therapies: indolent B-cell neoplasms (including CLL), aggressive B-cell neoplasms, and T- and NK-cell neoplasms. Subgroups and entities were defined according to the WHO classification, 4th edition,[1] which is largely compatible with ICD-O-3, used since 2001. The morphology of cases diagnosed during 1989-2000 was coded according

to ICD-O-2 and by using a combination of topography and morphology they were grouped as the entity closest to the original diagnosis (table 1). All unspecified cases were classified as aggressive B-cell neoplasms. Stage was not applicable for chronic lymphocytic leukemia, Waldenström macroglobulinemia, and cutaneous lymphoma. Year of diagnosis was divided into four periods (three of 5 years and one of 4 years): 1989-1993, 1994-1998, 1999-2003, and 2004-2007. For the period 1989-1994 survival data were only available for five (out of eight) regional cancer registries, i.e. CCC South, CCC Amsterdam, CCC West, CCC North-East and CCC East, all together serving 9 million people which are representative for the whole of the Netherlands. Patients younger than 15 years and older than 95 years were excluded from survival analysis. Mortality data for the period 1989-2008 were obtained from Statistics Netherlands without further morphology codes, being defined as C82-C85 of the ICD-10 classification from 1996 until 2008, and with the 200 and 202 codes of the ICD-9 classification till 1995. We therefore excluded patients with Waldenström macroglobulinemia, chronic lymphocytic leukemia, prolymphocytic leukemia, heavy chain disease, and hairy-cell leukemia from these analyses.

Statistical analyses

Annual incidence and mortality rates for the period 1989-2008 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardized to the European standard population (European Standardized Rates (ESR)). Changes were evaluated by calculating the estimated annual percentage of change (EAPC) and the corresponding 95% confidence interval. To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y=ax + b$ where $y = \ln(\text{rate})$ and $x =$ calendar year, then $EAPC = 100 * (e^{a-1})$). Incidence rates were also calculated for subgroup and sex. The proportional distribution of entities per subgroup was calculated by period of diagnosis.

Primary treatment was described as percentage of patients that received chemotherapy + radiotherapy, chemotherapy alone, radiotherapy alone, other therapies, no therapy and unknown therapy, for subgroup, stage, age and period. The use of targeted therapies including monoclonal antibodies was completely recoded by the cancer registry since 2007, in earlier years this registration was incomplete.

Traditional, cohort-based, relative survival analysis was applied for patients diagnosed during 1989-2007. Follow-up was available until January 1st, 2009. Therefore, 10-year relative survival of patients diagnosed in the period 1999-2003 and 5- and 10-year relative survival of patients diagnosed in the period 2004-2007 could not be calculated with this approach. To estimate these relative survival rates we used period-based relative survival analysis.[27] Survival trends were quantified as the mean annual percentage of change (MAPC) within 1989-2007 estimated by a linear regression model. A positive value of the mean implies an upward trend in survival (i.e. improving) and a negative value implies a negative trend (i.e. deterioration). Patients were censored at age 100 years at follow-up (N=20). SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

Results

Table 1 exhibits the number of patients for each entity of the non-Hodgkin lymphoma according to the WHO classification, newly diagnosed in the Netherlands during 1989-2007. Most common were diffuse large B-cell lymphoma (DLBCL) (N=16,079), chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL / SLL) (N=12,478) and follicular lymphoma (FL) (N=7,167). Fifty-five to 60 percent of all new patients were male, and the mean age of the whole group was 65 years (66 for indolent, 65 for aggressive, and 60 for T- and NK-cell). Fifty-seven percent of the patients was aged 65 years or older (57% for indolent, 58% for aggressive and 46% for T- and NK-cell). Neither distribution of gender nor age changed significantly over time (table 2). The proportion of patients with unknown stage decreased over time in al subgroups, parallel to a small shift towards higher stages.

Table 1: Number of patients with non-Hodgkin lymphoma according to WHO classification, 4th edition, in the Netherlands, 1989-2007

Subgroup	Entity name	Morphology code ICD-O-3	Morphology code ICD-O-2	Number of males	Number of females
Indolent B-cell	chronic lymphocytic leukaemia / small lymphocytic lymphoma	9823* 9670 9820	9592* 9800 9803	7393	5085
	B-cell prolymphocytic leukaemia	9833 9832	9825*	84	62
	splenic marginal zone lymphoma	9689		72	86
	hairy cell leukaemia	9940	9941	719	210
	lymphoplasmacytic lymphoma	9671[AA] 9761		1888	1339
	heavy chain disease	9762 9763		0	2
	extranodal marginal zone lymphoma	9699[BB] 9764	9671[A] 9672[D]	969	976
	nodal marginal zone lymphoma	9699[B]	9711	194	214
	follicular lymphoma, grade I-II	9690[CC] 9695[CC] 9691[CC]	9693[CC] 9694[CC]	3148	3185
	primary cutaneous follicle centre lymphoma	9690[C] 9695[C] 9691[C]	9693[C] 9694[C] 9675[C+##]	149	136
Aggressive B-cell	follicular lymphoma, grade III	9698	9697	420	414
	mantle cell lymphoma	9673	9672[DD]	1531	702
	diffuse large B-cell lymphoma (DLBCL)	9680[YY+##] 9684[YY+##] 9675[YY+##]	9593[YY+##] 9677[YY] 9681[YY] 9682[YY] 9712[YY]	8568	7511
	primary DLBCL of the CNS	9680[E+##] 9684[E+##] 9675[E+##] 9590[E+^^] 9591[E+##+^^]	9593[E+##] 9677[E] 9681[E] 9682[E]	506	443
	primary cutaneous DLBCL, leg type	9680[C+##] 9684[C+##]	9593[C+##] 9677[C] 9681[C] 9682[C] 9712[C]	191	235
	primary mediastinal large B-cell lymphoma	9679 9680[X+##] 9684[X+##] 9675[X+##]	9593[X+##] 9677[X] 9681[X] 9682[X]	28	46
	primary effusion lymphoma	9678		6	2
	Burkitt lymphoma	9687 9826		565	238
	other, unclassifiable B-cell neoplasms	9590[EE+^^] 9591[EE+##+^^] 9760 9596	9850 9595[^^] 9824	2007	1928

Subgroup	Entity name	Morphology code ICD-O-3				Morphology code ICD-O-2					Number of males	Number of females
T- and NK-cell	T-cell prolymphocytic leukaemia	9834				9825^					31	25
	T-cell large granular lymphocytic leukaemia	9831				9823^					23	17
	aggressive NK-cell leukaemia	9948									6	3
	adult T-cell leukaemia/lymphoma	9827									21	25
	extranodal NK/T-cell lymphoma, nasal type	9719				9713					67	37
	enteropathy-associated T-cell lymphoma	9717				9702[G]					98	70
	hepatosplenic T-cell lymphoma	9716									8	4
	subcutaneous panniculitis-like T-cell lymphoma	9708									6	10
	mycosis fungoides	9700									496	294
	Sézary syndrome	9701									20	22
	primary cutaneous T-cell lymphoma	9718	9593[#+C]			9714[#+C]					129	79
	peripheral T-cell lymphoma, nos	9702[GG]	9590^	9591^	9595^	9703	9704	9709			866	572
	angioimmunoblastic T-cell lymphoma	9705									148	136
	anaplastic large cell lymphoma	9714[CC]				9591[#]	9593[#]	9675[#]	9680[#]	9684[#]	360	244

Legend: Topographic inclusions or exclusions for that specific morphology code

[A] = <1-1-2001 than only C07, C08, C16-C20, C33, C34, C44, C69
[B] = only C77
[C]= only C44
[D] = only C07, C07, C16-C20, C33, C34, C44, C69
[E] = only C69.2-4, C71
[F] = only C40-41
[G] = only C17
[X] = only C37, C38.1-3

[AA] = <1-1-2001 than excl. C07, C07, C16-C20, C33, C34, C44, C69
[BB] = excl. C77
[CC] = excl. C44
[DD] = excl. C07, C07, C16-C20, C33, C34, C44, C69
[EE] = excl. C69.2-4, C71
[FF] = excl. C40-41
[GG] = excl. C17
[YY] = excl. C37, C38.1-3, C44, C69.2-4, C71

Tumour grade inclusions or exclusions for that specific morphology code

[#] = only grade 7
^ = only grade 5
* = only grade 6 or 9

[##] = excl. grade 7
[^^]= excl. grade 5

Table 2: Patient characteristics of non-Hodgkin lymphoma, by subgroup, in the Netherlands, during 4 periods in 1989-2007

Subgroup			1989-1993	1994-1998	1999-2003	2004-2007
Indolent B-cell	Number of patients		5476	6529	7337	6569
	Mean age		66.8	66.2	66	65.9
	Male sex		56%	58%	56%	56%
	Stage*	I	26%	27%	27%	25%
		II	12%	12%	12%	10%
		III	12%	12%	15%	15%
		IV	41%	42%	43%	47%
		Unknown	9%	7%	3%	3%
Aggressive B-cell	Number of patients		6083	6429	6738	6091
	Mean age		64.7	64.3	64.9	65.7
	Male sex		53%	54%	55%	56%
	Stage	I	28%	28%	27%	25%
		II	18%	18%	19%	18%
		III	12%	13%	15%	18%
		IV	30%	31%	34%	35%
		Unknown	12%	10%	5%	4%
T- and NK-cell	Number of patients		843	936	1028	1010
	Mean age		59.6	58.5	59.6	61.1
	Male sex		64%	57%	59%	60%
	Stage*	I	26%	25%	24%	21%
		II	14%	17%	16%	14%
		III	15%	17%	19%	27%
		IV	30%	31%	35%	34%
		Unknown	15%	11%	6%	5%

Legend: *exclusion of chronic lymphocytic leukaemia, Waldenström macroglobulinemia, and cutaneous lymphoma, because stage was not applicable.

Trends in incidence and mortality

Between 1989 and 2007 the incidence of all non-Hodgkin lymphomas has been rising significantly from 19 to 22 per 100,000 for males and from 12 to 14 for females (figure 1) (EAPC 0.5% (95%CI: 0.2 - 0.8) and 1.0% (95%CI: 0.7 - 1.3), respectively). Mortality remained stable until 2003 (ESR 6.2), to decrease thereafter significantly (EAPC -5.2% (95%CI: -7.2 - -3.2) (figure 1), resulting in and mortality rate of 4.8 in 2008. Figure 2 shows that the rise in incidence for all NHL was mainly due to changes in indolent mature B-cell neoplasms (EAPC 0.8% (95%CI: 0.3 - 1.3) for males and 1.9% (95%CI: 1.5 - 2.3) for females) and of mature T- and NK-cell neoplasms

(EAPC 0.9% (95%CI: -0.1 - 1.9) for males and 2.0% (95%CI: 1.0 - 3.0) for females). The incidence of aggressive mature B-cell neoplasms remained stable between 1989 and 2007. Increasing incidence and decreasing mortality resulted in a prevalence of 17.597 at January 1st, 2008.

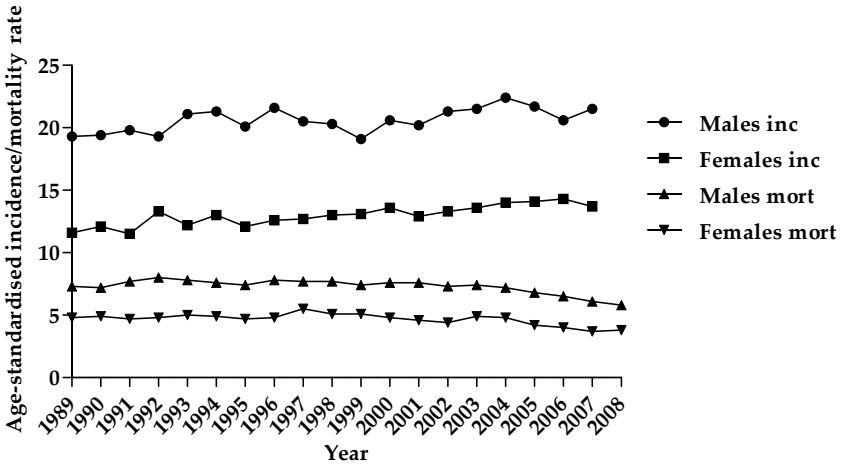


Figure 1: Trends in age-standardized incidence and mortality rates (ESR) of non-Hodgkin lymphoma, by sex, in the Netherlands, 1989-2008

Legend: inc= incidence, mort= mortality.

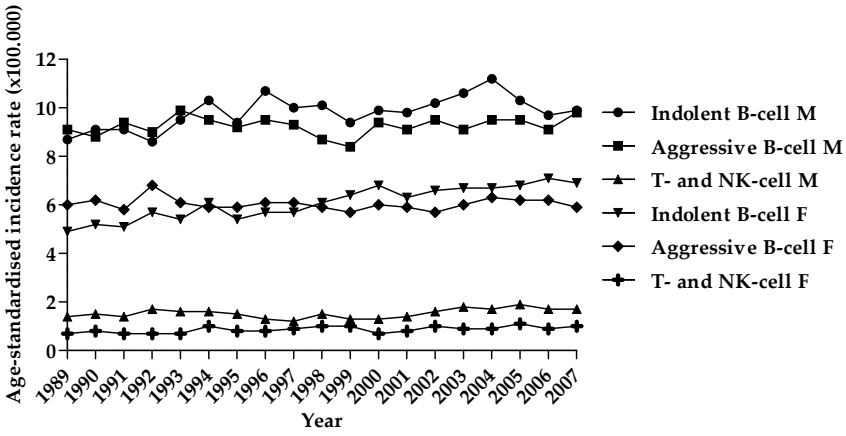


Figure 2: Age-standardised incidence rates (ESR) of non-Hodgkin lymphoma, by subgroup and sex, in the Netherlands, 1989-2007

Legend: M= males, F= females.

Trends in the proportions of entities in subgroups of lymphoma

Within the group of indolent lymphoma, the proportion of CLL/SLL was higher among males, whereas the proportion of FL was higher among females. The percentage of CLL/SLL has been decreasing from 52% to 48% for males and from 49% to 43% for females (figure 3A). In contrast, the proportion of FL rose from 21% to 23% for males and 26% to 30% for females. Furthermore, the percentage of lymphoplasmatic lymphoma has been decreasing, while extranodal marginal zone lymphoma increased. Within the group of aggressive lymphoma the proportion of mantle cell lymphoma (MCL) increased among males and DLBCL increased among both males and females (figure 3B). The proportion of unclassifiable B-cell neoplasms decreased from 20% to 7% for males and 20% to 9% for females. Within the group of T- and NK-cell lymphoma the proportion of peripheral T-cell lymphoma, NOS and mycosis fungoides declined while those for primary cutaneous T-cell lymphoma, angioimmunoblasic T-cell lymphoma, and anaplastic large cell lymphoma for both males and females increased (figure 3C).

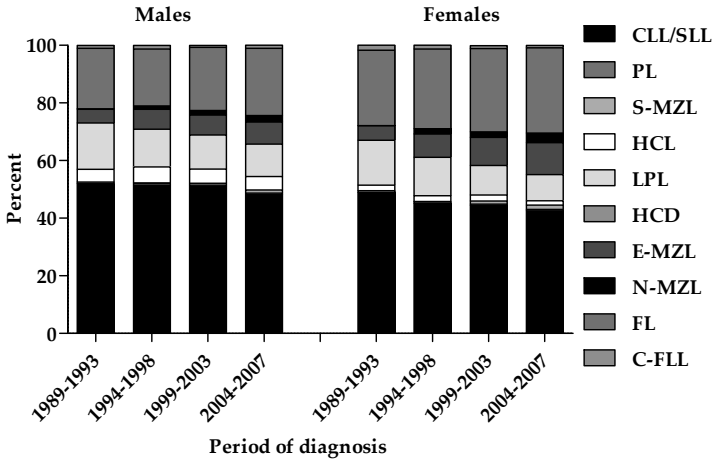
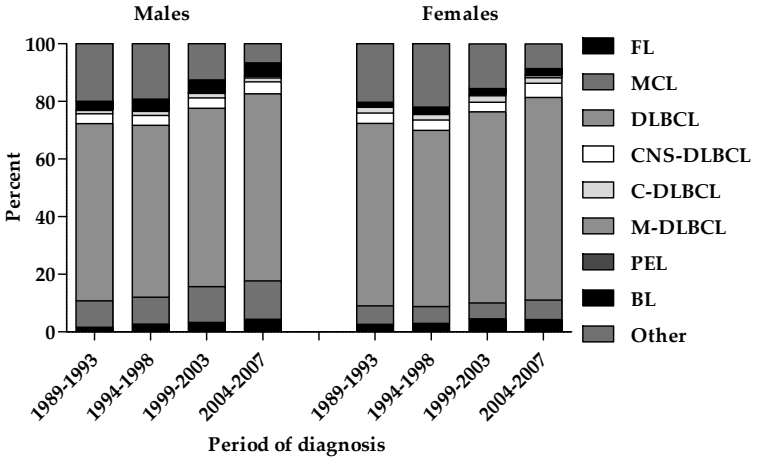


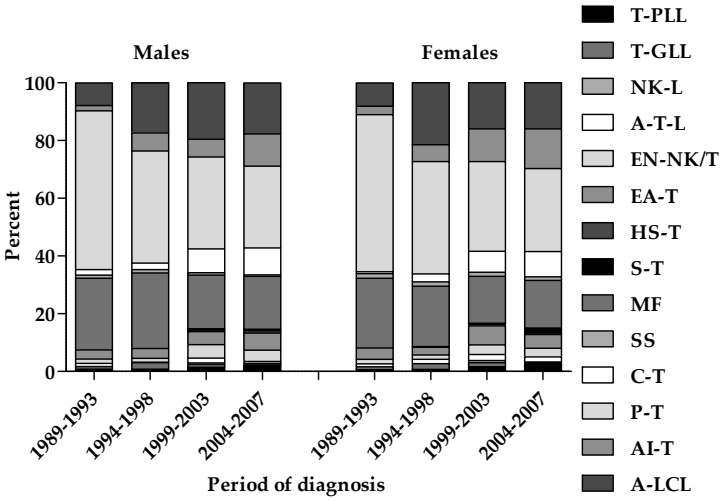
Figure 3: Trends in proportional distribution of NHL entities per subgroup, period and sex, in the Netherlands, 1989-2007
A: Indolent B-cell

Legend: CLL/SLL= chronic lymphocytic leukaemia/small lymphocytic lymphoma, PL= B-cell prolymphocytic leukaemia, S-MZL= splenic marginal zone lymphoma, HCL= hairy cell leukaemia, LPL= lymphoplasmacytic lymphoma, HCD= heavy chain disease, E-MZL= extranodal marginal zone lymphoma, N-MZL= nodal marginal zone lymphoma, FL= follicular lymphoma, grade I-II, C-FLL= primary cutaneous follicle centre lymphoma.



B: Aggressive B-cell

Legend: FL= follicular lymphoma, grade III, MCL= mantle cell lymphoma, DLBCL= diffuse large B-cell lymphoma, CNS-DLBCL= primary DLBCL of the CNS, C-DLBCL= primary cutaneous DLBCL, leg type, M-DLBCL= primary mediastinal large B-cell lymphoma, PEL= primary effusion lymphoma, BL= Burkitt lymphoma, other= other, unclassifiable B-cell neoplasms.



C: T- and NK-cell

Legend: T-PLL= T-cell prolymphocytic leukaemia, T-GLL= T-cell large granular lymphocytic leukaemia, NK-L= aggressive NK-cell leukaemia, A-T-L= adult T-cell leukaemia/lymphoma, EN-NK/T= extranodal NK/T-cell lymphoma, nasal type, EA-T= enteropathy-associated T-cell lymphoma, HS-T= hepatosplenic T-cell lymphoma, S-T= subcutaneous panniculitis-like T-cell lymphoma, MF= mycosis fungoides, SS= Sézary syndrome, C-T= primary cutaneous T-cell lymphoma, P-T= peripheral T-cell lymphoma, nos, AI-T= angioimmunoblastic T-cell lymphoma, A-LCL= anaplastic large cell lymphoma.

Trends in therapy

The proportion of patients with indolent B-cell neoplasms receiving chemotherapy was slightly lower in 2004-2007 (33%) compared to earlier time periods (36%), whereas the proportion wait and see policy increased over time (figure 4A). During 2007, 16% of indolent (20% in patients below 65 years of age and 12% for the elderly) and 52% of aggressive B-cell neoplasms (61% in patients younger than 65 years of age and 46% among the elderly) received a targeted therapy as primary treatment. Patients with stage I aggressive disease received more chemotherapy + radiotherapy (from 17% to 38%) and less radiotherapy alone in the later time periods (figure 4B). In patients with advanced stage aggressive B-cell and T- and NK-cell neoplasms the percentages of patients receiving chemotherapy did not change over time (figure 4B and 4C). The change in the proportions of radiotherapy and chemotherapy for indolent B-cell and stage I aggressive B-cell disease was similar in patients younger and older than 65 years. However, in all subgroups elderly patients were treated less aggressively than younger patients (data not shown).

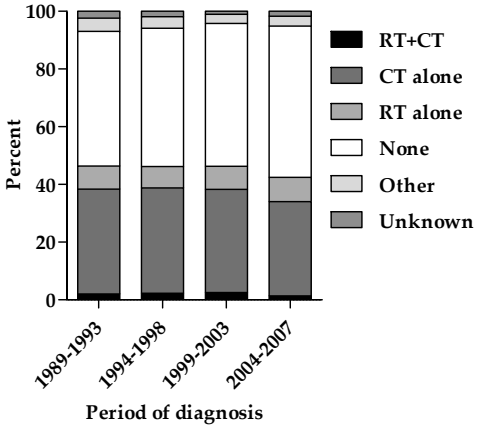
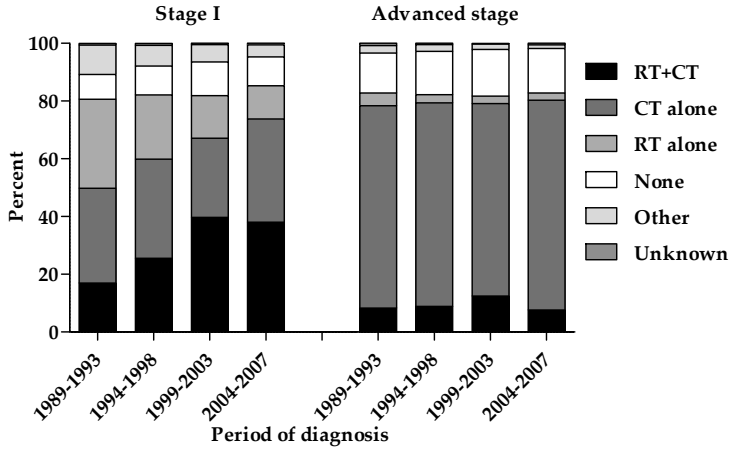
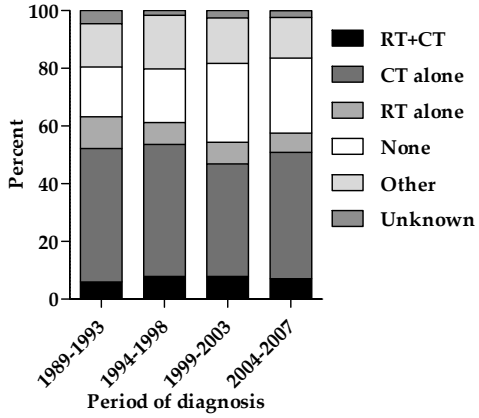


Figure 4: Trends in primary treatment of non-Hodgkin lymphoma, by subgroup, period and stage, in the Netherlands, 1989-2007
A: Indolent B-cell



B: Aggressive B-cell



C: T- and NK-cell

Legend: CT= chemotherapy, RT= radiotherapy

Trends in survival

Five-year relative survival of patients with mature B-cell neoplasms has improved, for those with indolent lymphoma rising from 67 to 75% and for aggressive from 43% to 52%, but remained stable for patients with T- and NK-cell neoplasms (48%). Patients older than 65 years had a worse relative survival compared to those younger than 65 years (figure 5). In indolent B-cell neoplasms relative survival gradually changed from 78% to 83% and 59% to 68%, respectively, for patients younger and older than 65 years, resulting in a statistically significant MAPC of 0.5% (95%CI:

0.3-0.8) and 1.0% (95%CI: 0.6-1.4). The 5-year relative survival rates for patients with aggressive B-cell neoplasms aged <65 years and aged 65+ changed from 54% to 66% and 35% to 41%, respectively. Survival for these patients was stable until 1996 for younger patients and until 2000 for elderly patients. Afterwards, relative survival rose significantly, MAPC 2.4 and 4.1, respectively for patients younger and older than 65. In T- and NK-cell neoplasms survival was stable around 54% in younger patients (<65 years), and decreasing from 46% to 37% in patients aged 65 or older, especially between 1989 and 2004, MAPC -3.6 (95%CI: -5.8 - -1.4).

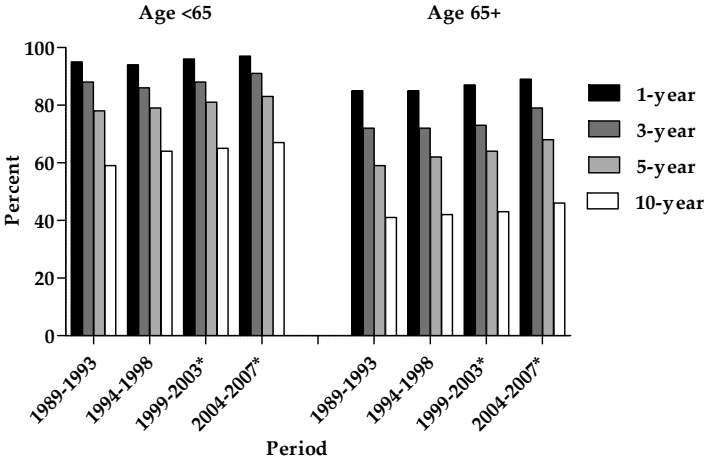
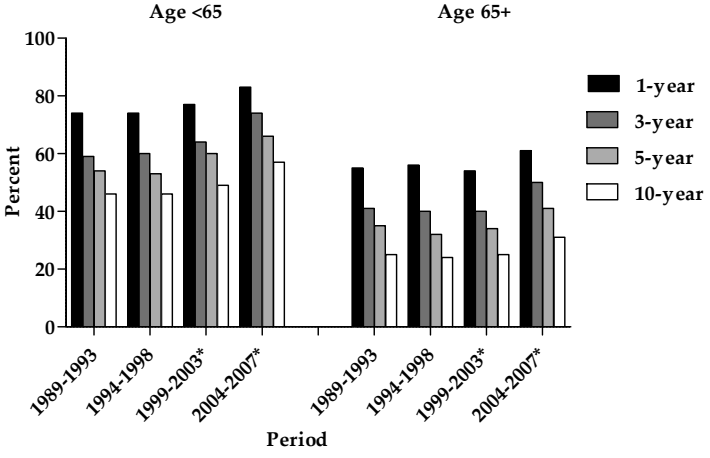
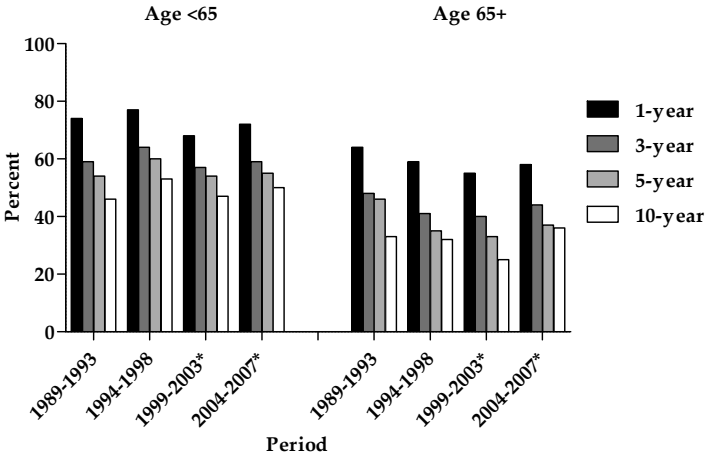


Figure 5: Trends in relative survival for patients with non-Hodgkin lymphoma, by subgroup, period and age, the Netherlands, 1989-2007
A: Indolent B-cell



B: Aggressive B-cell



C: T- and NK-cell

Legend: * 10-years relative survival of period 1999-2003 and 5- and 10-years relative survival of period 2004-2007 are estimated by period analyses (others are calculated by cohort analyses).

Discussion

Since 1989 the incidence of indolent B-cell neoplasms and T- and NK-cell neoplasms increased modestly but significantly and remained stable for aggressive B-cell neoplasms. Mortality from NHL was stable between 1989 and 2003, and has been decreasing since 2003. Five-year relative survival has improved for mature B-cell neoplasms, but remained stable for T- and NK-cell neoplasms.

Incidence rates in our study were similar to other studies in Europe.[18,28] For several decades, there has been an increase in NHL incidence worldwide,[3,4,29-32] which was confirmed in the Dutch population. Furthermore, it is particularly due to the rise in incidence in indolent B-cell and T- and NK-cell neoplasms. We included all unspecified cases with the group of aggressive B-cell neoplasms, because it was most likely that these unspecified cases belonged in this subgroup. Due to improvements in diagnostic tools, less unspecified cases were documented in recent time periods. Without the decrease in unspecified cases, the incidence of aggressive B-cell neoplasms would probably also have increased. Literature showed that the rise in incidence was especially seen between 1960 and 1990; subsequently the incidence has declined in for example Sweden, Denmark and the USA.[28,29] Our study showed a smaller rise in incidence, but leveling off was not visible (yet). Little is known about

the risk factors for this group of malignancies. Some risk factors have been indentified for NHL overall or one of several NHL subtypes: immunodeficiency disorders, immunosuppression, some infectious agents like Epstein Barr Virus (EBV), some autoimmune disorders and a positive family history of haematolymphoproliferative malignancies.[29,33] Most of the autoimmune and chronic inflammatory disorders exhibited a growing prevalence in the population,[34] which could partly explain the rise in lymphoid neoplasms. Furthermore, advances in diagnostic techniques, like flow cytometric methods, could have led to better detection of CLL.[18] On the other hand, the numerous coding and classification changes over time may have exerted some influence on the time trends.

The increase in mortality until the early nineties and the later stabilization and decline was seen all over the world.[3,28,31] Since 2003 mortality is decreasing, probably due to smaller increases in incidence and improving survival rates in the subtypes with the highest prevalence. Prevalence of NHL was 11,143 in 2000,[35] and increased to 17.548 at January 1st, 2008.

The high proportion of CLL/SLL, FL, and DLBCL is well known from earlier studies.[36,37] The trends in proportional distribution of subtypes showed that unclassifiable B-cell neoplasms and peripheral T-cell lymphoma, not otherwise specified (NOS) decreased over time. Classification has thus been improving through better histological, molecular-biological and immunofenotypical techniques.[18]

It is of interest that Dutch indolent B-cell neoplasms patients received less chemotherapy than for instance in Ireland (36% vs. 63%), less radiotherapy (8% vs. 27%) and more wait and see policy (49% vs. 13%),[38] largely explained by the inclusion of CLL patients. Up to 40% of patients with stage I aggressive B-cell neoplasm received the advised combination of radiotherapy and chemotherapy (albeit aimed at only 30% of patients >65 years, and 50% <65 years). Especially in the first period, the number of patients receiving radiotherapy alone was very high (31%). Twenty percent of the patients with advanced stage aggressive non-Hodgkin lymphoma did not receive primary chemotherapy and older patients also received less radiotherapy; this has been confirmed by others.[37-40] Our study reported on the use of chemotherapy and radiotherapy in everyday clinical practice. T- and NK-cell neoplasms have a low prevalence in the Netherlands and treatment of the entities differs. Our study indicated that 50% of these patients received chemotherapy.

Survival was within the range of earlier documentations of population-based studies in Europe.[6-8,28,38] Our study not only confirms previous findings of the improved survival of patients with non-Hodgkin lymphoma,[36,38] but also showed an amelioration during 2004-2007. As survival of non-Hodgkin lymphoma is influenced by subtype, age, stage, and therapy,[36,38,41] the improved survival of B-cell neoplasm in the latest period is most likely explained by the increased use of more effective drugs such as anti-CD20 monoclonal antibodies (rituximab).[11-17] Nonetheless, the effect of new therapies on survival is expected to be smaller in everyday practice than in trials, because not all patients are eligible for this therapy and the regimen needs to be adapted.[37] We found that in 2007 only 16% of patients with an indolent B-cell neoplasm and 52% with an aggressive B-cell neoplasms received targeted therapy. Especially in elderly patients such treatment may be waived, e.g. in the presence of severe co-morbidity.[37] The improvement in survival in the elderly patients with aggressive B-cell neoplasms was indeed smaller, and started later. More accurate diagnostics and/or prognostic tools (e.g. International Prognostic Index (IPI)), aim to promote tailored treatment, and thus also better survival.[11,13,15,20,36] Better supportive care could also affect survival in patients with mature B-cell neoplasms[42] through better endurance of therapy and also quality of life.[43] Then, improvements in the treatment of a concomitant condition like HIV, even though its prevalence in the Netherlands was relatively low, may have added since the end of the 90's.[6] Finally, there has been an overall pattern of more and better use of the treatment guidelines both centrally and regionally through the Dutch-Belgium Cooperative Group for Haemato-Oncology (HOVON) and the CCC's. The proportional distribution of entities in the subgroup of T- and NK-cell neoplasms appeared to have changed considerably over time. A population-based Italian study exhibited higher relative survival rates than in our study,[36] due the higher proportion of mycosis fungoides with its much better prognosis. In 2009, consensus statements were formulated to improve diagnosis, staging, follow-up and treatment approaches for these patients.[22]

Since 1985, HOVON (www.hovon.nl) has been conducting many randomized clinical trials with high participation rates to test new therapies and improve survival of lymphoma patients in the Netherlands. Currently, almost 25 studies for NHL are in progress, which is likely to bring further progress, also in the quality of care to all patients.

Several limitations require consideration; First of all, an evolving classification system, improvements in disease detection and evolving cancer registration procedures may have contributed to temporal trends in incidence of subgroups.[18] Therefore, we also reported the trends in incidence of all NHL combined, with the proportional changes of each entity. Secondly, despite the rather clinical nature of the Dutch cancer registry, lack of details regarding applied treatments and dose adherence in our population-based registry limited the potential to explore and elucidate specific reasons for the observed changes in survival. Finally, 10-year relative survival of 1999-2003 and the 5- and 10-year survival of 2004-2007 were estimated by period analysis to provide more up-to-date insight in recent long-term trends, but as treatment changes permanently, comparison with real observed (cohort) relative survival measurements can be ambiguous.

In conclusion, in the Netherlands, incidence of indolent mature B-cell and mature T- and NK-cell neoplasms has increased, but remained stable for aggressive neoplasms since 1989. Survival increased for all mature B-cell neoplasms, preceding a declining mortality and increased prevalence of NHL (17,597 at January 1st, 2008).

Acknowledgements

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2.2

Improving relative survival, but large remaining differences in survival for non-Hodgkin lymphoma across Europe and the US during 1990-2004

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Abstract

Background

Non-Hodgkin lymphoma (NHL) is the most common haematologic malignant neoplasm in adults. Monitoring differential changes in population-based survival across Europe and the United States (US) could point to progress attained and impact of application of novel treatments.

Patients and Methods

We examined trends in age-specific 5-year relative survival among NHL patients aged 15 years and older between 1990-1994 and 2000-2004, based on follow-up data from 12 population-based cancer registries across Europe, using period analysis techniques and compared the results with similar trends of NHL patients in the US, as recorded in the SEER database.

Results

By 2000-2004, overall 5-year relative survival of patients with NHL across Europe was between 37% and 62%, achieved by overall increases in 5-year relative survival ranging from 4 to 12 percent units between 1990-1994 and 2000-2004. Changes in age-specific survival ranged from -1 to 43 percent units during the same time interval. For NHL patients older than 55, relative survival in individual European registries was the hole period between 8 and 36 percent units lower than in the US, theoretically representing a lag of 4 to 10 years of progress.

Conclusions

Our analyses disclosed a strong and ongoing increase in long-term survival for NHL patients in European populations. The geographic differences potentially indicate that further improvements could be possible, especially for patients aged 55 and older. The presumptive delay in improvement in survival among elderly NHL patients in Europe remains to be clarified.

Introduction

Non-Hodgkin lymphoma (NHL) is the most common haematologic malignant neoplasm in adults in almost all populations worldwide.[1,2] Over the last decades, the incidence of NHL has been rising in Europe and North America. Mortality rose until the mid 1990s, and started to level off or decline in the following decade.[1,3]

As early detection programs for NHL are currently not available, improvements in survival can be expected to occur mainly due to the application of novel treatment strategies. Since 1997, breakthrough clinical studies have shown that combining rituximab to standard chemotherapy regimens resulted in a major clinical benefit (increased response rate, progression free and overall survival) in several NHL subtypes, without substantial toxicity.[4-12] Monoclonal antibodies were first approved for treatment of NHL in 1997 in the United States and subsequently across Europe, then being advised in treatment guidelines for several common subtypes of NHL.[13]

These new and expensive therapies urges to disclose the most recent trends in survival. Traditional methods for calculating population-based cancer survival estimates, such as cohort and complete analyses, are less suitable for monitoring recent changes in survival, given that these estimates largely reflect the survival experience of patients diagnosed many years ago. Period analysis have shown to provide up-to-date long-term survival estimates by exclusively considering survival experience of cancer patients in a recent calendar period.[14]

We now describe up-to-date trends in relative survival of NHL, using data from population-based cancer registries involved in the EUNICE survival cooperation from various parts of Europe, with special attention to age-specific and geographical differences also with the United States (US).

Patients and Methods

Study population and data collection

The EUNICE database contains data from 12 European population-based cancer registries. The project, data preparation, and inclusion criteria for survival analysis were described in detail before.[15] For this analysis we selected all patients aged 15 years and older, newly diagnosed with NHL (N=70,743). NHL was defined as the

C82-C85 codes of the ICD10 classification in 1985 to 2004, for all registries except for Finland and Norway, that used registry specific morphology codes. Patients were grouped into five major age groups: 15 to 44, 45 to 54, 55 to 64, 65 to 74 and 75 years and older.

In order to disclose more detailed trends in survival, we additionally grouped the European cancer registries into 2 separate categories, i.e. Central European registries (Cracow, Estonia and Lithuania) and Western European registries, in order to reflect overall health expenditure differences. For comparison with age specific relative survival for NHL patients in the United States, we relied on data from the study by Pulte et al.,[16] which were derived using the 1973-2004 limited-use database of the Surveillance, Epidemiology and End Results (SEER) Program.

Statistical analysis

Age group specific 5-year relative survival estimates were calculated for calendar periods 1990-1994, 1995-1999 and 2000-2004, using a saturated Poisson regression model for relative survival in which the logarithms of the excess number of deaths were modelled as a function of follow-up year (categorical variable), using the logarithm of the person-time at risk as the offset.[17] The obtained survival estimates were used to derive overall age-adjusted 5-year relative survival estimates, with weights from the International Cancer Survival Standards (ICSS).[18]

Relative survival, which may be interpreted as disease-specific survival within a cancer patient population (without having to rely on causes of death from death certificates), was derived as the ratio of observed survival of the cancer patients and the expected survival of a comparable, age and sex matched group of the underlying general population.[19] Expected survival, based on registry-specific life tables, was calculated according to the Ederer II method.[20] All derived relative survival estimates were period estimates, which are exclusively based on the survival experience of patients during the specific calendar period for which they are derived.[14] These have been shown to closely predict survival later observed for patients diagnosed in that period.[21,22] To derive a test for survival trends, the above Poisson model was extended to include calendar period (1990-1994, 1995-1999, 2000-2004) as a numerical variable. For the registries with data on incident cases up to 2003 (Estonia, Slovenia, and Tuscany), but follow-up until 2004, the analysis followed the principles of the hybrid analysis.[23]

Due to the greater number of patients in the grouped analysis, we could perform geographical comparisons including age and sex-specific relative survival analyses for more detailed periods of time (calendar periods: 1990-1992, 1993-1995, 1996-1998, 1999-2001 and 2002-2004). For overall comparisons between the 2 groups of European registries and the United States, for each age group, adjustment for sex was made by deriving weighted averages of sex-specific 5-year relative survival estimates, with weights from the age-group specific proportions of the grouped Western European registries.

Results

Patient Characteristics

Numbers of cases by registry, calendar period, sex and age group are shown in table 1. The overall number of cases of NHL increased over time, from 14,567 in 1990-1994 to 19,657 in 2000-2004. The mean age of patients ranged between 60 and 65 years in the registries and increased from 63 in 1990-1994 to 65 in 2000-2004 (data not shown). The numbers of cases were largest in age groups 65-74 and 75+ (both 27%). Sex was equally distributed in the registries, except a male preponderance in Turin, Eindhoven and Geneva.

Survival trends in NHL, individual cancer registries

Between 1990-1994 and 2000-2004, 5-year age-standardized relative survival of patients diagnosed with NHL increased in all participating registries by 4 to 12 percent units (table 2). In 2000-2004, the highest overall 5-year relative survival was seen in Saarland, Geneva and Turin (above 60%), and the lowest survival (below 41%) was seen in Cracow, Estonia and Lithuania; elsewhere relative survival was between 52% and 56%.

Table 1. Numbers of patients with non-Hodgkin lymphoma by participating registry, calendar period, sex and age group

Registry	N	Calendar period (year)					Sex		Age group (years)				
		1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	Men	Women	15-44	45-54	55-64	65-74	75+
Cracow	896	91	85	161	258	301	454	442	105	138	224	258	171
Estonia**	1867	246	270	328	532	491	961	906	265	237	453	551	361
Lithuania*	2591	0	0	544	815	1232	1288	1303	420	338	632	735	466
Slovenia**	3530	378	546	761	934	911	1714	1816	539	467	737	960	827
Turin	3331	0	540	781	941	1069	1782	1549	373	403	705	960	890
Tuscany**	3795	0	691	971	1186	947	1982	1813	469	432	828	1038	1028
Eindhoven***	3340	283	265	347	1048	1397	1863	1477	487	501	712	877	763
Scotland	17307	2407	3031	3565	4092	4212	8421	8886	1897	2033	3441	4945	4991
Finland	16724	2052	2659	3521	4092	4400	8139	8585	1970	2265	3362	4505	4622
Norway	13084	1687	2247	2692	2884	3574	6864	6220	1547	1639	2423	3432	4043
Geneva	1416	200	275	290	299	352	758	658	201	189	294	302	430
Saarland	2862	384	445	606	656	771	1434	1428	388	377	671	755	671
Total	70743	7728	11054	14567	17737	19657	35660	35083	8661	9019	14482	19318	19263

Legend: * Registration started in 1990, ** Registration of patients untill 2003, *** Survival data was completed for a larger area of this region since 1995 (+- twice the region)

In all registries, survival was highest in the two youngest age groups and lowest in the oldest age group (table 3). In 2000-2004, the difference between survival for the age group with the best and worst prognosis ranged between 53 percent units (in Cracow) and 22 percent units (Turin).

Table 2. Age-standardised period estimates of 5-year relative survival of patients with non-Hodgkin lymphoma, by participating registry and calendar period.

Registry	1990-1994		1995-1999		2000-2004		Diff
	PE	SE	PE	SE	PE	SE	
Cracow	28	10.8	35	8.2	37	7.6	8.7
Estonia	32	7.7	39	6.0	38	4.9	5.9
Lithuania	36	8.3	38	5.1	41	3.9	4.1
Slovenia	43	5.1	51	4.4	55	3.9	11.6
Turin	49	4.9	52	4.0	61	3.8	11.7
Tuscany	45	4.0	52	3.6	56	3.4	11.8
Eindhoven	47	8.8	48	4.8	52	3.4	5.3
Scotland	42	2.1	45	2.0	54	2.0	11.7
Finland	44	2.1	48	1.9	54	1.8	10.5
Norway	50	2.5	51	2.3	56	2.1	6.6
Geneva	49	7.1	48	7.3	61	6.3	12.1
Saarland	53	5.7	52	5.2	62	4.3	8.8

Legend: PE = period estimate of survival, SE = standard error, Diff = difference (percent units) between 1990-1994 and 2000-2004.

Differences in the rise in survival varied generally much stronger between age groups than between registries (table 3). In the Central European countries and Saarland relative survival only improved in the younger age groups, in Scotland in all age groups, while in Finland and Norway in 4 out of 5 age groups. In Slovenia, Turin and Tuscany marked rises occurred in patients aged 55 to 64, and to a lesser extent also 65-74 years. Additionally, in Slovenia there was a strong improvement in survival for the youngest age group, while in Tuscany survival also increased for the oldest age group. In Eindhoven, relative survival only improved for patients aged 45 to 54, and in Geneva for the 2 youngest and the oldest age group.

Table 3. Period estimates of 5-year relative survival of patients with non-Hodgkin lymphoma, by participating registry, age group and calendar period.

Registry	Age group	1990-1994		1995-1999		2000-2004		Diff	P value
		PE	SE	PE	SE	PE	SE		
Cracow	15-44	26	13.0	42	11.4	74	8.8	48.4	0.001
	45-54	35	11.7	55	8.4	67	9.1	31.8	0.110
	55-64	39	8.6	42	7.3	40	6.6	1.4	0.433
	65-74	18	9.7	31	8.3	28	5.3	10.0	0.508
	75+	27	12.9	24	7.8	21	9.7	-6.0	0.589
Estonia	15-44	37	7.9	51	6.6	70	5.5	33.6	<0.001
	45-54	28	7.1	62	7.4	52	6.7	23.5	0.050
	55-64	37	5.7	44	5.4	38	4.6	1.1	0.514
	65-74	42	7.0	39	5.1	41	4.2	-1.5	0.977
	75+	19	10.1	23	6.6	23	5.0	3.2	0.696
Lithuania	15-44	35	12.5	54	4.8	71	3.7	36.2	<0.001
	45-54	42	7.0	50	6.2	60	4.6	17.5	0.002
	55-64	33	10.1	40	4.1	50	3.5	17.0	0.007
	65-74	34	6.2	35	4.3	32	3.2	-1.5	0.727
	75+	41	8.5	32	6.3	27	4.7	-13.7	0.710
Slovenia	15-44	66	4.5	64	4.2	78	3.7	11.5	0.040
	45-54	60	5.6	64	5.0	68	4.1	8.6	0.277
	55-64	42	4.2	59	4.1	62	3.9	20.3	<0.001
	65-74	42	4.8	53	3.8	52	3.3	10.4	0.088
	75+	32	5.9	34	5.1	39	4.3	7.0	0.105
Turin	15-44	63	5.4	72	4.4	66	4.7	3.4	0.774
	45-54	68	5.0	65	4.9	71	4.3	3.3	0.484
	55-64	50	4.3	58	3.9	68	3.5	18.5	0.001
	65-74	45	4.4	54	3.7	61	3.2	16.5	0.002
	75+	42	5.6	34	4.0	49	4.2	6.9	0.242
Tuscany	15-44	68	4.4	61	4.2	71	3.9	3.4	0.566
	45-54	64	5.0	76	4.1	74	4.0	10.1	0.122
	55-64	54	4.0	61	3.3	70	3.1	15.8	0.001
	65-74	45	3.8	49	3.2	54	3.2	9.1	0.040
	75+	23	3.8	35	3.9	37	3.4	14.2	0.021

Registry	Age group	1990-1994		1995-1999		2000-2004		Diff	P value
		PE	SE	PE	SE	PE	SE		
Eindhoven	15-44	71	7.9	70	4.1	77	3.2	6.2	0.207
	45-54	57	8.4	58	4.8	71	3.6	14.2	0.038
	55-64	53	8.4	45	4.7	57	3.2	4.5	0.408
	65-74	42	8.3	46	4.3	48	3.2	6.3	0.925
	75+	37	10.0	41	5.5	38	3.8	0.9	0.208
Scotland	15-44	64	2.4	69	2.3	75	2.3	10.2	0.001
	45-54	63	2.6	59	2.3	72	2.1	9.3	0.003
	55-64	49	2.1	53	2.0	58	1.9	8.9	0.001
	65-74	37	1.8	42	1.8	52	1.8	15.3	<0.001
	75+	27	2.1	29	1.9	38	2.0	11.8	<0.001
Finland	15-44	74	2.2	78	2.0	78	2.1	4.1	0.287
	45-54	62	2.6	67	2.0	74	1.9	11.6	<0.001
	55-64	53	2.2	55	2.0	65	1.8	11.6	<0.001
	65-74	41	2.0	45	1.8	52	1.7	10.8	<0.001
	75+	24	2.0	31	2.0	34	1.9	10.4	<0.001
Norway	15-44	64	2.5	64	2.6	81	2.4	16.7	<0.001
	45-54	68	2.9	65	2.4	70	2.2	1.4	0.423
	55-64	58	2.6	60	2.5	67	2.0	8.2	0.013
	65-74	46	2.2	51	2.2	55	2.1	8.6	<0.001
	75+	35	2.4	33	2.2	38	2.1	3.0	0.010
Geneva	15-44	51	6.8	72	6.8	79	6.8	27.4	0.006
	45-54	64	8.3	72	7.2	83	5.8	19.0	0.083
	55-64	61	7.2	47	7.3	70	5.4	9.1	0.429
	65-74	49	7.4	45	7.6	56	6.3	6.3	0.660
	75+	32	6.2	35	7.2	46	7.0	13.6	0.013
Saarland	15-44	66	5.7	79	4.4	84	3.9	17.9	0.011
	45-54	62	5.5	66	5.5	84	4.1	21.7	0.005
	55-64	62	4.6	52	4.7	67	3.9	5.2	0.173
	65-74	53	5.3	54	4.4	56	4.3	3.0	0.179
	75+	39	7.0	38	6.4	49	4.8	9.9	0.715

Legend: PE = period estimate of survival, SE = standard error, Diff = difference (percent units) between 1990-1994 and 2000-2004, P value is for the trend over time.

Survival trends in NHL, by grouped registries and comparison to the US

Table 4 and figure 1 show age-specific survival trends by 3-year periods and grouped cancer registries. In 2002-2004, survival for the youngest age group was similar in the 3 population groups (Central European (registries of Cracow, Estonia and Lithuania), Western European (all other registries of the EUNICE Survival working group) and the US). Patients aged 45-54 exhibited similar survival rates in Western Europe and the US, but Central European registries had a poorer survival. However, for NHL patients aged 55 and older, survival was consistently highest in the US, followed by Western European registries and Central European registries, for all periods and both sexes. For patients older than 75, survival for the grouped Western European populations in 2002-2004 was similar to that in the United States in 1990-1992. For patients aged 65-74, survival for Western Europe in 2002-2004 was similar to survival for the US in 1993-1998. For patients aged 55-65, this was 1996-2001 Sex-specific analyses indicate that women had better or similar survival than men, in all three groups of populations. Sex differences in survival were less pronounced in the European populations than in the US and decreased over time.

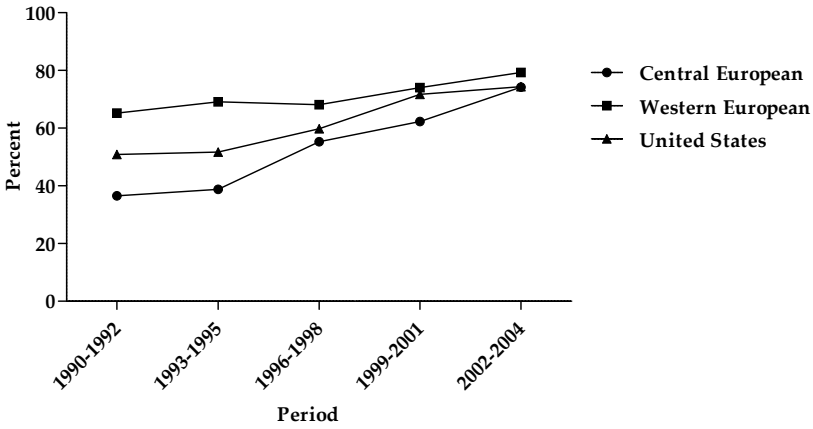
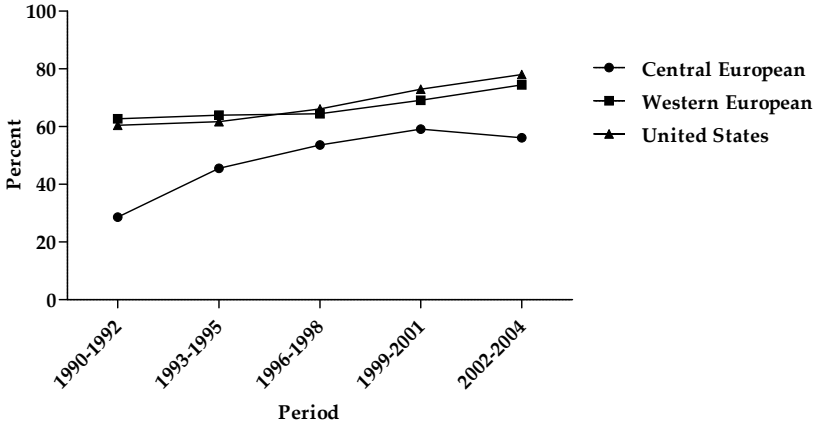
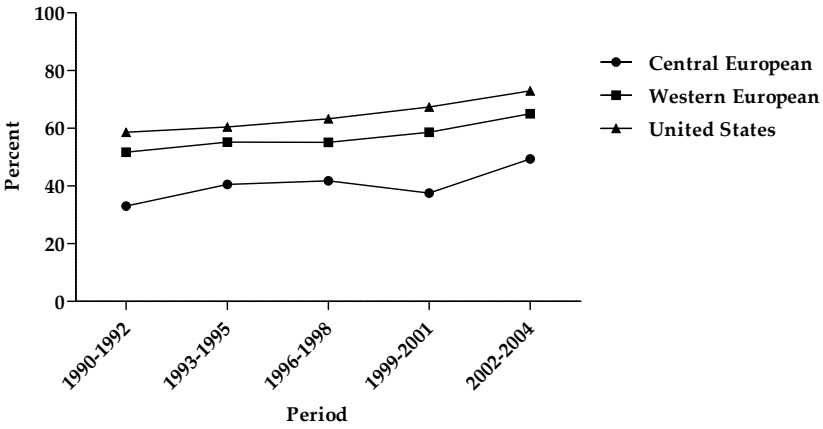


Figure 1. Sex-standardised period estimates of 5-year relative survival of patients with non-Hodgkin lymphoma, by age group, calendar period and grouped registries.

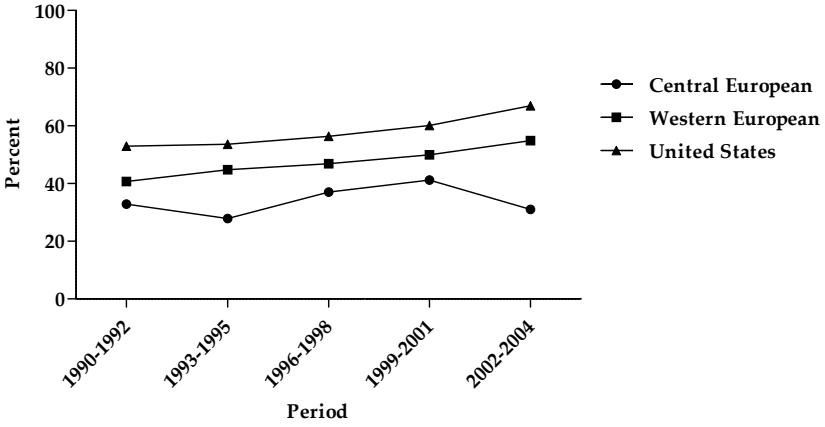
A: Age group 15-44



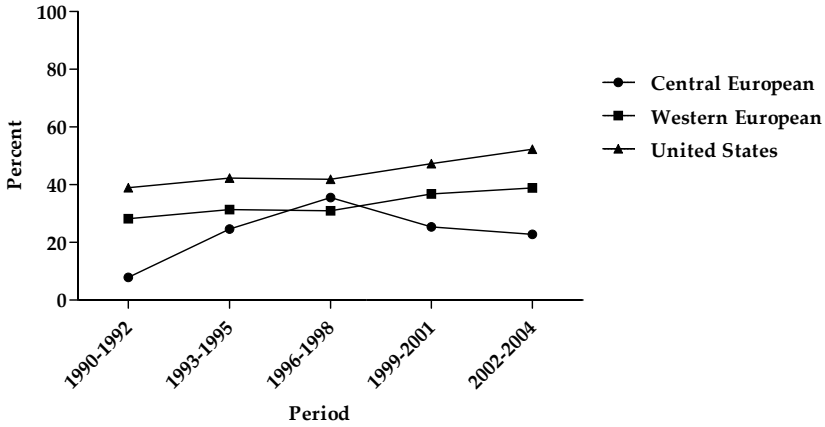
B: Age group 45-54



C: Age group 55-64



D: Age group 65-74



E: Age group 75+

Table 4. Period estimates of 5-year relative survival of patients with non-Hodgkin lymphoma, by grouped registries, age group and calendar period.

Registry group	Age group	1990-1992		1993-1995		1996-1998		1999-2001		2002-2004		Diff	P value
		PE	SE	PE	SE	PE	SE	PE	SE	PE	SE		
Central	15-44	31	9.0	40	7.8	56	6.6	60	5.3	74	4.9	43.0	<0.001
European	45-54	25	8.1	28	6.9	50	8.4	53	6.4	53	6.2	28.0	0.172
Men	55-64	27	6.8	26	5.6	36	5.6	37	4.7	48	5.2	21.6	0.001
	65-74	24	10.0	24	5.6	29	5.8	38	5.3	21	3.6	-2.7	0.151
	75+	4	8.8	15	11.3	29	8.8	23	7.6	19	6.0	14.8	0.836
Central	15-44	46	8.4	38	10.2	54	6.6	66	6.0	75	5.5	29.6	0.005
European	45-54	33	10.1	69	8.2	58	7.4	67	7.0	60	6.6	26.9	0.304
Women	55-64	41	7.7	57	7.0	48	5.2	39	4.6	51	4.7	10.1	0.435
	65-74	42	9.5	32	5.4	45	5.6	44	4.5	41	4.0	-1.0	0.862
	75+	11	6.9	32	8.9	40	8.0	27	6.3	26	4.6	15.0	0.521
Western	15-44	62	2.0	66	1.9	65	1.8	72	1.8	78	1.7	16.1	<0.001
European	45-54	59	2.4	58	2.1	62	1.9	67	1.8	73	1.7	14.0	<0.001
Men	55-64	51	2.0	52	1.9	50	1.8	53	1.7	63	1.6	11.4	<0.001
	65-74	38	1.9	42	1.9	44	1.7	46	1.6	51	1.6	12.9	<0.001
	75+	26	2.3	28	2.3	31	2.2	35	2.1	40	2.0	13.8	<0.001
Western	15-44	70	2.3	74	2.2	73	2.1	77	2.1	82	2.0	11.2	0.002
European	45-54	67	2.6	71	2.2	68	2.1	72	1.9	76	1.8	8.8	0.007
Women	55-64	52	2.1	59	2.0	61	1.8	65	1.7	68	1.6	15.6	<0.001
	65-74	43	1.8	48	1.7	49	1.6	54	1.6	59	1.5	15.5	<0.001
	75+	30	1.9	34	1.8	31	1.6	38	1.7	38	1.5	8.5	<0.001
United	15-44	39	1.3	40	1.3	52	1.4	68	1.4	71	1.4	31.9	<0.001
States	45-54	54	1.8	54	1.7	61	1.6	68	1.5	75	1.4	20.6	<0.001
Men	55-64	54	1.7	56	1.7	60	1.7	64	1.6	70	1.4	15.4	<0.001
	65-74	48	1.7	52	1.7	56	1.6	55	1.6	64	1.6	15.4	<0.001
	75+	41	2.4	40	2.1	38	1.9	46	1.9	50	1.9	9.2	<0.001

Registry group	Age group	1990-1992		1993-1995		1996-1998		1999-2001		2002-2004		Diff	P value
		PE	SE	PE	SE	PE	SE	PE	SE	PE	SE		
United	15-44	69	2.0	70	1.9	72	1.8	77	1.7	79	1.6	10.6	<0.001
States	45-54	69	2.3	71	2.0	73	1.9	80	1.6	83	1.5	13.6	<0.001
Women	55-64	64	1.8	65	1.9	70	1.8	72	1.6	77	1.5	13.1	<0.001
	65-74	58	1.7	56	1.6	57	1.6	65	1.6	70	1.5	12.5	<0.001
	75+	38	1.7	44	1.7	45	1.6	49	1.6	54	1.6	16.2	<0.001

Legend: PE = period estimate of survival, SE = standard error, Diff = difference (percent units) between 1990-1992 and 2002-2004, P value is for the trend over time.

When comparing age-specific estimates for specific European populations for 2000-2004 with estimates derived for the US for 2002-2004, there was no population in Europe for which survival would have been higher than in the US. In all age groups, differences were more than 20 percent units lower in the Central European registries, than in the US. At the same time, only 6 registries in western Europe (Turin, Tuscany, Finland, Norway, Geneva and Saarland) exhibited a survival within 0 to 5 percent units of the estimate for US males in the age group 55-64, and only 1 and 3 such registries in the age groups 65-74 and 75+ (Turin in both groups and Geneva and Saarland in the latter, respectively). For all other registries, estimates were between 5 and 20 percent units lower for the age group 65-74 and between 10 and 20 percent units lower in the age group 75+, when compared to the US.

Discussion

In the European cancer registries included in this analysis, the overall 5-year relative survival of patients with NHL varied between 37% and 62% in 2000-2004. These levels of survival were achieved after increases in survival between 4 and 12 percent units since 1990-1994. During the same interval, changes in age group specific survival were much more heterogeneous, ranging between -1 and 43 percent units. Younger patients experienced a remarkably improved survival in the Central European registries, resulting in similar relative survival in all geographical groups in the latest time period. For NHL patients older than 55, relative survival in European registries was, with only a few exceptions, overall between 10 and 36 percent units lower than for patients recorded in the United States SEER database in the same time period. This theoretically represents an overall average lag of at least 4 to 10 years of progress, if judged against the pace of progress seen in the study period.

The improvement in survival and geographical differences during the examined periods could be explained by several factors, as listed below. First of all, survival could have improved by the advances in therapy in recent years. The introduction of monoclonal antibody therapy in combination with chemotherapy [5-10,24,25] has likely played a role for the most recent years. It is important to point out that recently introduced monoclonal antibody therapy could only partly explain the higher relative survival for older American NHL patient:[16] also in the era before monoclonal antibodies, considerable differences in survival were present between in European

registries and the US. Monoclonal antibodies were first approved for use in NHL in 1997 in the United States; in Europe, this therapy was introduced between 1997 and 2001.[13] Since addition of rituximab was shown to increase response rates in elderly only in 2002, its introduction was later in this age group with subsequent delayed improvement in survival.[11,12] Implementation of innovations in medicine always takes time and available data indicates that during this study period and beyond, rituximab utilization has been continuously rising in several populations of this study.[13,26] Overall, it is likely that rituximab did not have a major effect on survival before 2002 in most of the examined population. In the period prior to rituximab, several changes in chemotherapy regimens have been investigated. This could have caused improvement in survival and differences between countries.[27,28] The lack of details regarding applied treatments and dose adherence in most population-based refrains us from estimating specific effects on survival.

The second reason for both improved survival as well as differences between regions are improvements in the general clinical care, resulting in a better treatment of HIV, stem cell transplantation, better antibiotic therapy, improvements of supportive care (which enables intensified treatment and better quality of life), higher enrollment in clinical trials, international collaboration, and better use of treatment guidelines by multidisciplinary working groups.[16,29]

Health expenditures and level of access to health care are important overall determinants of health outcomes and could therefore also result in survival differences between regions.[13] The total national expenditure on health per year per capita (1994-2002) ranged from 4251 to 427 US$ within Europe.[30] Differences in overall health expenditures and level of access to health care between Central and Western parts of Europe may largely explain the differences in relative survival between those areas. However, Western European cancer registries are situated in countries with a largely comparable socioeconomic status as the United States. Therefore, overall socioeconomic differences and availability of resources for health care between these countries and the US should not be the main determinants of survival differences seen in this study, even if survival estimates for SEER patients may potentially be somewhat higher than survival in the US as a whole.[31,32]

The coding of lymphoma has also been different between regions. However we studied the total group of NHL instead of the different entities. Survival is different

for every morphology group of which the distribution could have been different in the regions. We could not differentiate between these morphology groups in our study, but previous comparison of the morphology and coding of lymphoid cancers between EUROCARE3 and SEER data did not affect the survival results dramatically.[33] Furthermore, a subdivision of the youngest age group was not possible because of small numbers. This would have been helpful because of potential shifts with increasing age in the proportion of aggressive and indolent lymphomas.[34] In addition, the proportion of microscopic verification could have been different between countries, as was seen in the study of Gatta et al.[29]

Finally, differences between registries also require careful consideration. Some of the registries were comprehensive for a country (Estonia, Lithuania, Slovenia, Scotland, Finland, Norway), others only for a region (Cracow, Turin, Tuscany, Eindhoven, Geneva, Saarland) or sample of the population of that country (SEER database in the US).[15] Sampled or regional estimates may not always be representative for an entire country, e.g. SEER estimates were generally a little higher than US estimates based on larger coverage of the US population,[35] to which the general usage of national life tables for SEER estimates also contributes.[31] However, these factors are not likely to explain more than 1-3% units of difference in survival. Relative survival for European registries always was calculated using the expected survival of the population in that region (except for Cracow, for which national life tables were used), which thereby corrects for differences in general mortality. Registry specific differences in data availability, with Lithuania contributing data from 1990 onwards, while Estonia, Slovenia and Tuscany provided data until 2003 only resulted in estimates with higher standard errors in these periods, while we compensated for data availability using hybrid analyses.[23] Furthermore, the Eindhoven Cancer registry also covered an adjacent, expanded area since 1995 with presumably the same case-mix. These changes in case numbers over time, are unlikely to have had a major influence on survival estimates and trends. Although, minor differences might have occurred in completeness of registration and of follow-up ascertainment, we do not expect subsequent major differences in survival.[36-38] If any, the total effect of these changes are much smaller than the survival differences seen in this study (which often reached or exceeded 10 percent units). Moreover, our data came from long standing and good quality cancer registries.

Our study confirms previous findings of major differences in survival of NHL patients between European populations and between European populations and the US, exhibiting ongoing improvements in the early 21st century, in all populations studied.[15,16,39-42] Survival differences between European populations and the US persisted, especially in older patients. Main determinants for the presumptive delay in improvement in survival by many years, especially in elderly NHL patients in Europe remain to be elucidated in order to reduce both the survival differences within Europe, as well as the lag in progress with the United States.

In conclusion, our analyses disclosed a strong and ongoing increase in long-term survival for NHL patients in European populations served by dedicated cancer registries. Nevertheless, the geographic differences indicate that survival for NHL patients can further improve in Europe, especially for patients aged 55 and older. The reasons for the presumptive delay in improvement in survival among elderly NHL patients in Europe compared to the United States remain to be better clarified.

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Chapter 3

Aetiology

3.1

Excess of autoimmune and chronic inflammatory disorders in patients with lymphoma compared with all cancer patients: a cancer registry-based analysis in the south of the Netherlands

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Abstract

Background

We investigated the association between autoimmune and chronic inflammatory disorders and several cancer types including lymphomas.

Patients and methods

All cancer patients diagnosed between 1995 and 2007, aged 15 to 90 years, and registered in the Eindhoven Cancer Registry were included in this study. Co-morbidity at diagnosis was recorded by qualified registry personnel who obtained the information from the clinical record. We determined the prevalence of rheumatoid arthritis (RA), chronic inflammatory bowel diseases, connective and vascular tissue diseases, ulcers of the stomach and duodenum, hepatitis, human immunodeficiency virus (HIV), and tuberculosis (TBC) among newly diagnosed patients with lymphoma and compared this with the prevalence among patients with all other cancers.

Results

The prevalence of most of these co-morbidities was higher in patients with lymphomas than those with other malignancies. RA was more often present in newly diagnosed patients with most lymphomas, ulcers of stomach and duodenum in patients with marginal zone lymphoma, hepatitis in case of diffuse large B-cell lymphoma, HIV with aggressive B-cell lymphoma, and TBC with mantle cell lymphoma.

Conclusions

This study confirms the positive association between autoimmune and chronic inflammatory disorders and the various lymphoproliferative malignancies, suggesting either a shared etiology or pathogenesis or a direct causal relation. This is a fairly new method to study aetiological questions about cancers in a population-based cancer registry.

Introduction

Since the 70's, the incidence of lymphomas has been rising in Europe and North America,[1-3] subsequently levelling off in for example Sweden, Denmark and the USA since 1990.[4] Lymphoproliferative malignancies comprise heterogeneous groups of malignancies with markedly different biological and clinical features. The exact aetiology is largely unknown for the majority of these entities, and therefore the increase in incidence is still difficult to elucidate.

Positive associations have been revealed between certain lymphomas and inflammation, autoimmune disease and infectious agents.[5] This relationship has been described in case-control studies,[6,7] cohort studies,[8] reviews,[9-11] and expert opinions.[12] However, considering the inherent heterogeneity and rarity amongst both autoimmune and chronic inflammatory disorders and lymphomas, it has been challenging to identify significant associations.[11]

Infectious agents causing lymphomas can be classified according to several mechanisms. First, some viruses can directly transform lymphocytes. Second, immunodeficiency is associated with a high risk for some non-Hodgkin lymphoma (NHL) subtypes. Third, some infections increase lymphoma risk through chronic immune stimulation,[13] which is also present in autoimmune diseases. Treatment of autoimmune and chronic inflammatory disorders could also affect the risk of lymphoproliferative malignancies. Another reason for the association could be shared environmental risk factors,[6] and in some autoimmune diseases genetic mutations are discovered, which also lead to lymphoproliferation.[14]

Co-morbidity of cancer patients is most commonly used to study treatment differences and prognostic influences,[15] but co-morbidity can also be used to study its association with malignancies in a cancer registry [16] by comparing the prevalence of autoimmune and chronic inflammatory disorders among lymphoma patients with other cancer patients.

Patients and methods

Study population and data collection

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.4 million inhabitants, 10 general hospitals and two large radiotherapy institutes.[17] Trained registration clerks actively collect data on patient characteristics, diagnosis, topography, histology, stage and information about initial treatment (delivered within 6 months of diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status.[18]

Since 1993 the Eindhoven Cancer Registry also records the presence of serious co-morbidity with prognostic impact at the time of cancer diagnosis, based on a slightly modified version of the widely used Charlson co-morbidity index.[19,20] Co-morbidity was defined as any chronic disease that was present at the time of cancer diagnosis and documented in the patient's medical record. Co-morbidities were registered as dichotomous variables (yes/no), according to the medical history of the patient, the use of relevant drugs and diagnostic work-up.

Autoimmune and chronic inflammatory disorders included in this registry are: rheumatoid arthritis (RA), chronic inflammatory bowel diseases (IBD), connective and vascular tissue diseases (CTD), ulcers of the stomach and duodenum (UL), hepatitis (HEP), human immunodeficiency virus (HIV), and tuberculoses (TBC). IBD includes M. Crohn, colitis ulcerosa and inflammatory bowel disease. CTD includes autoimmune and chronic inflammatory disorders in the connective and vascular tissue: sarcoïdosis (M. Besnier Boeck), Wegener's disease, periarteriitis nodosa, and systemic lupus erythematodus.

The prevalence of these disorders was calculated for the total group of all haematological malignancies and for subgroups of lymphoproliferative malignancies: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). NHL being subdivided into T-cell NHL and B-cell NHL (indolent and aggressive). In the B-cell NHL group we identified as separate entities chronic lymphocytic leukaemia (CLL), marginal-zone lymphoma (MZL), lymphoplasmacytic lymphoma (WAL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), as well as multiple myeloma (MM), following the WHO classification. For comparison, the prevalence among all cancer patients together and the major cancer subgroups (breast, lung, prostate, colon and rectum cancer) was calculated.

Statistical analysis

We calculated a relative risk (RR) of a specific malignancy compared to all cancers combined, for each autoimmune or chronic inflammatory disorder, adjusted for age and sex. If the RR of a specific cancer site exceeded one, than the risk for this specific cancer among those with autoimmune or chronic inflammatory disorder was higher than for all other cancer types. For these cancer types it is likely that the autoimmune or chronic inflammatory disorder was thus associated with this specific cancer type. We used the major cancers (colon, rectum, lung, breast, and prostate) as a comparison to the haematological malignancies. Since these major cancer groups represent a large part of the control group (all cancers combined) the RR of these major subgroups is expected to be closer to that of the reference group.

All patients with cancer newly diagnosed between 1995 and 2007, aged 15 to 90 years, and recorded in the Eindhoven Cancer Registry were included (N=117,481). Patients with cancer diagnosed at autopsy were not selected.

The SAS computer package (version 9.1, SAS Institute Inc., Cary, North Carolina, USA, 1999) was used for statistical analyses.

Results

The prevalence of the autoimmune and chronic inflammatory disorders in the newly diagnosed cancer populations (table 1) varied between 7.6% and 0%. The prevalence was higher for lymphomas than the other cancers, but variation between subgroups of NHL existed (figure 1). The details are described below.

Rheumatoid arthritis (RA)

The prevalence of RA ranged from 1% to 4.2% between the specific cancer types. The RR for lung cancer and most lymphoproliferative malignancies was higher than for other cancers. This effect was not significant for the haematological entities CLL, MZL, MCL and MM. Newly diagnosed patients with colon cancer less often had RA.

Chronic inflammatory bowel disease

The prevalence of chronic inflammatory bowel disease (IBD) ranged from 0 percent to 0.85 percent. IBD was significantly associated with colon cancer (RR=1.9). IBD exhibited a slightly positive association with DLBCL. Breast cancer was negatively associated with IBD.

Table 1: Prevalence of autoimmune or chronic inflammatory disorders as co-morbidity in newly diagnosed patients with solid tumours and haematological malignancies

	N	RA		IBD		CTD		UL		HEB		HIV		TBC	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
All cancers	117481	1298	1.28	479	0.47	215	0.21	3375	3.33	774	0.76	55	0.05	1524	1.5
Colon	10571	97	1.02	58	0.61	19	0.2	334	3.52	66	0.69	0	0	155	1.63
Rectum	6022	53	0.97	34	0.62	11	0.2	156	2.85	26	0.47	0	0	68	1.24
Lung	17038	283	1.78	80	0.5	30	0.19	728	4.59	117	0.74	2	0.01	387	2.44
Breast	19125	217	1.29	48	0.29	40	0.24	191	1.14	64	0.38	1	0.01	175	1.04
Prostate	13051	104	0.93	44	0.4	22	0.2	341	3.06	49	0.44	3	0.03	135	1.21
Haematological	7515	139	2	40	0.58	27	0.39	276	3.98	73	1.05	21	0.3	143	2.06
HL	567	7	1.3	2	0.37	2	0.37	5	0.93	8	1.49	1	0.19	8	1.49
NHL	5704	120	2.28	29	0.55	20	0.38	229	4.35	60	1.14	19	0.36	115	2.19
T NHL	268	8	3.39	2	0.85	3	1.27	10	4.24	4	1.69	0	0	5	2.12
B NHL	5436	112	2.23	27	0.54	17	0.34	219	4.36	56	1.11	19	0.38	110	2.19
Indo B	2088	40	2.08	9	0.47	8	0.42	86	4.47	16	0.83	0	0	24	1.25
CLL	1032	12	1.27	4	0.42	1	0.11	39	4.13	7	0.74	0	0	9	0.95
MZL	218	3	1.52	0	0	1	0.51	15	7.58	1	0.51	0	0	0	0
WAL	152	6	4.2	0	0	0	0	10	6.99	2	1.4	0	0	4	2.8
FL	631	17	2.89	5	0.85	4	0.68	20	3.4	6	1.02	0	0	11	1.87
Aggres B	2082	56	2.9	11	0.57	7	0.36	90	4.66	32	1.66	19	0.98	58	3
DLBCL	1288	37	3.09	10	0.84	7	0.59	64	5.35	19	1.59	11	0.92	38	3.18
MCL	246	5	2.19	0	0	0	0	12	5.26	2	0.88	2	0.88	9	3.95
MM	1214	16	1.42	7	0.62	2	0.18	42	3.74	7	0.62	0	0	28	2.49
Extra nodal	655	18	2.96	3	0.49	1	0.16	42	6.91	2	0.33	3	0.49	12	1.97

Legend: Haematological = all haematological malignancies, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma, T NHL = T-cell NHL, B NHL= B-cell NHL, Indo B = indolent B-cell NHL, Aggres B = aggressive B-cell NHL, CLL = chronic lymphocytic leukaemia, MZL = maginal-zone lymphoma, WAL = lymphoplasmacytic lymphoma, FL = follicular lymphoma, DLBCL = diffuse large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma, Extra nodal = extra nodal lymphoma, RA = rheumatoid arthritis, IBD = chronic inflammatory bowel disease, CTD = connective and vascular tissue diseases, UL = ulcers of the stomach and duodenum, HEP = hepatitis, HIV = human immunodeficiency virus, TBC = tuberculosis.

Connective and vascular tissue diseases

The prevalence of connective and vascular tissue diseases (CTD) ranged from 0% to 1.3%. Haematological malignancies and the lymphoproliferative subgroups NHL, T-cell NHL, FL, and DLBCL were associated with connective and vascular tissue disease. This disease was not only associated with B-cell, but also with T-cell NHL.

Ulcers of the stomach and duodenum

The prevalence of ulcers of the stomach and duodenum ranged from 0.9% to 7.6%. It was especially high for newly diagnosed patients with lung cancer, haematological malignancies, and the lymphoma subgroups of NHL, B-cell NHL, indolent and aggressive B-cell NHL, MZL, WAL, DLBCL and extranodal lymphoma. Ulcers less often occurred in newly diagnosed patients with rectum, breast, and prostate cancer. The association of MZL and extranodal lymphoma was more pronounced than that of the other lymphomas.

Hepatitis

The prevalence of hepatitis ranged from 0.4% to 1.7%. Hepatitis was associated with haematological malignancies, and the subgroups NHL, B-cell NHL, aggressive B-cell NHL and DLBC and negatively associated with rectum, breast and prostate cancer.

HIV

The prevalence of HIV ranged from 0% to 1%. HIV was significantly associated with haematological malignancies, especially with the lymphoproliferative subgroups NHL, B-cell NHL, aggressive B-cell NHL, DLBCL, MCL, MM and extra nodal lymphoma. The effect was most pronounced for aggressive B-cell NHL.

Tuberculosis

The prevalence of TBC ranged from 0% to 4.0%. TBC was associated more often with lung cancer, haematological malignancies, and the subgroups HL, NHL, B-cell NHL, aggressive B-cell NHL, DLBCL, MCL and MM, than with other types of cancer. TBC was negatively associated with prostate cancer.

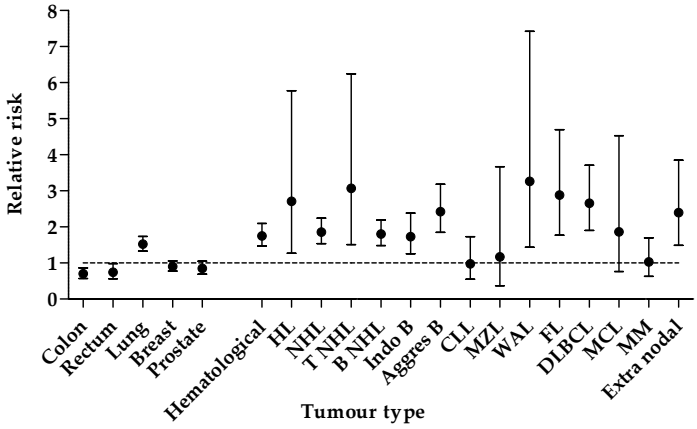
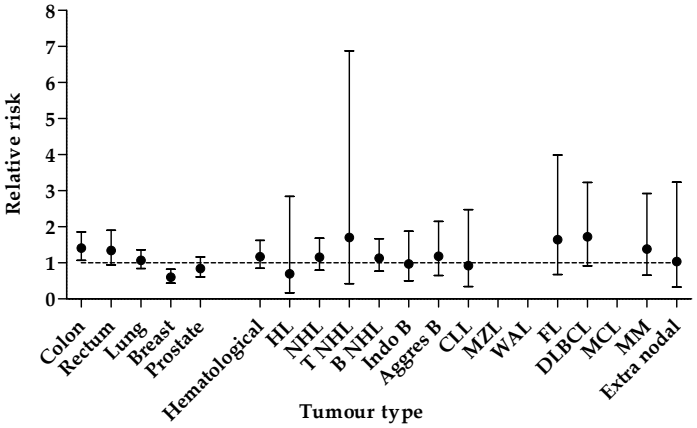
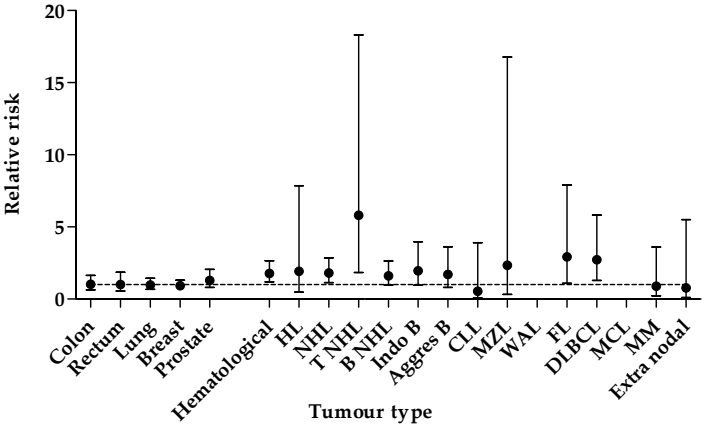


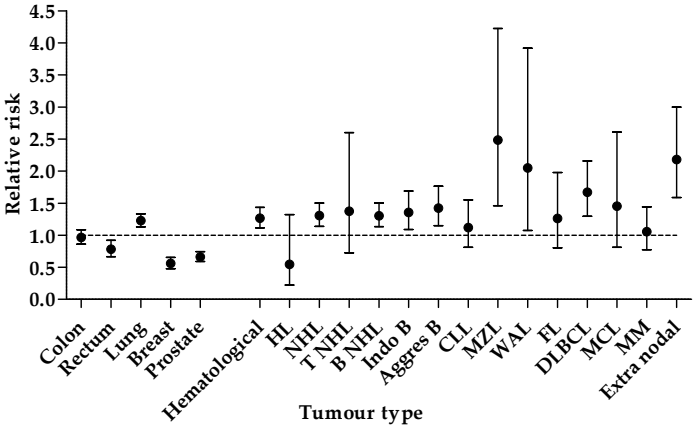
Figure 1: Relative risk of specific cancer versus all cancers (RR=1) for autoimmune and chronic inflammatory disorders as co-morbidity, adjusted for sex and age.
A: Rheumatoid arthritis



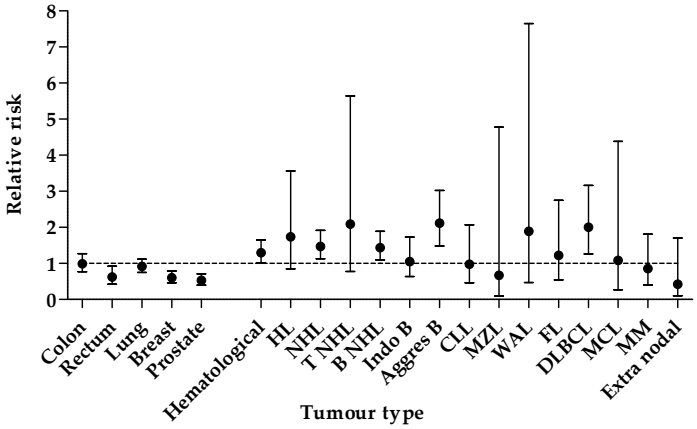
B: Chronic inflammatory bowel disease (M. Chron, colitis ulcerosa and inflammatory bowel disease)



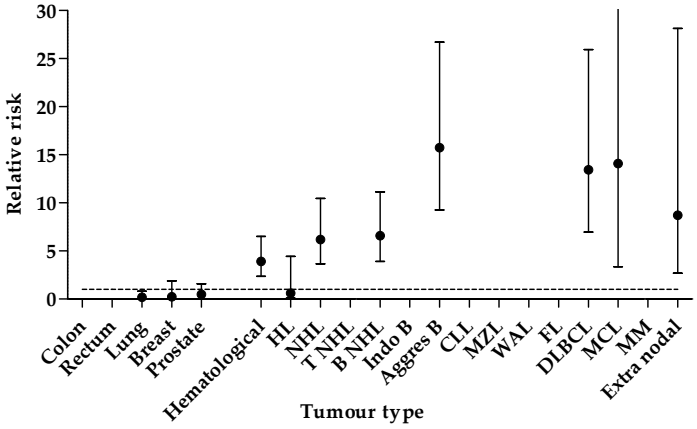
C: Connective and vascular tissue diseases (sarcoïdosis (M. Besnier Boeck), Wegener, periarteriitis nodosa, and systemic lupus erythematosus)



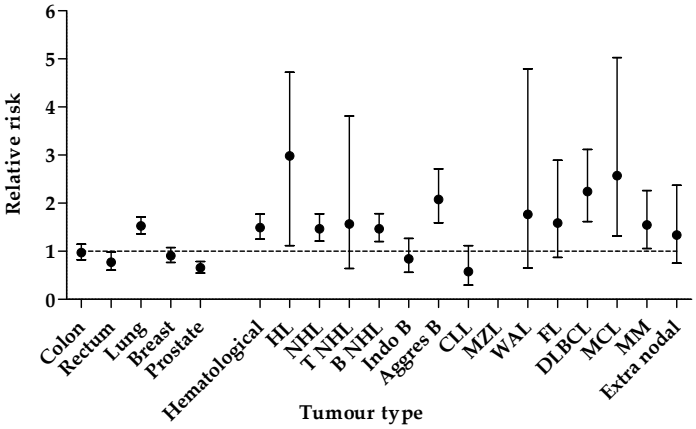
D: Ulcers of the stomach and duodenum



E: Hepatitis



F: HIV



G: Tuberculosis

Legend: Haematological = all haematological malignancies, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma, T NHL = T-cell NHL, B NHL= B-cell NHL, Indo B = indolent B-cell NHL, Aggres B = aggressive B-cell NHL, CLL = chronic lymphocytic leukaemia, MZL = maginal-zone lymphoma, WAL = lymphoplasmacytic lymphoma, FL = follicular lymphoma, DLBCL = diffuse large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma, Extra nodal = extra nodal lymphoma
The vertical lines represent the 95% confidence intervals.

Discussion

In general, the prevalence of autoimmune and chronic inflammatory co-morbidities was higher among newly diagnosed patients with lymphoproliferative malignancies than with the various common cancers. Especially the positive association between RA and most lymphomas, ulcers of stomach and duodenum and marginal zone lymphoma, hepatitis and diffuse large B-cell lymphoma, HIV and aggressive B-cell lymphoma, and TBC and mantle cell lymphoma was striking.

The National Institute for Public Health and the Environment has published prevalence rates of several autoimmune and infectious diseases for the general Dutch population,[21] based on general practitioner registration systems. The life time prevalence of the autoimmune and chronic inflammatory disorders in the general population was comparable or even higher than in our study. Although the presence of co-morbidity was assessed from medical records, which is more precise than self-reported or administrative databases, we could have missed less severe and unrecorded co-morbidities. Because we used the other cancer types as control group, with the same registration of co-morbidity, registration bias was unlikely in

this study. Furthermore, the registration system of our study is population-based and that of the general practitioner registration systems is a sample of the population, which could hamper comparison of the two systems. In addition, the age distribution differs between cancer patients and people in the general population.

As known from literature infectious agents causing lymphomas can be classified, according to several mechanism of action. First, some viruses can directly transform lymphocytes; for example Epstein Barr virus (EBV). Second, human immunodeficiency virus (HIV) is unique in causing profound depletion of CD4+ T lymphocytes, leading to acquired immunodeficiency syndrome and an associated increased risk for some non-Hodgkin lymphoma (NHL) subtypes. Third, some infections might increase lymphoma risk through chronic immune stimulation, and therefore greater activation of lymphatic cells.[6,13,22] Indeed, lymphoma in autoimmune diseases might also be caused by chronic immune stimulation due to deregulated lymphocyte reactivity against self-antigens and the production of auto-antibodies. Certain treatments of autoimmune or chronic inflammatory disorders could also affect the risk of certain subtypes of cancer.[6,23,24] Furthermore, certain immunosuppressive medications, for example in IBD, could lead to consequently reduced immune surveillance.[7] These last two mechanisms could interfere with each other, and therefore a balance in therapy is warranted.[25] Immune dysregulation of T- and B-cell mediated immune responses, as in immune deficiencies, can also lead to autoimmunity, autoinflammation and lymphoma.[26] Another reason for the association could be shared environmental risk factors, like smoking, [6] and in some autoimmune diseases genetic mutations are discovered which also lead to lymphoproliferation. [14] Finally, investigation of lymphadenopathy in autoimmune or chronic inflammatory disorders might lead to earlier detection of a haematological malignancy.

Rheumatoid arthritis

The prevalence of RA in the Dutch population varies between 1 percent and 3.7 percent according to age and sex,[21] similar to the prevalence in our study. The diagnosis of autoimmune and chronic inflammatory disorders is difficult and this could have led to misclassification, for example some RA patients could have had Sjögrens disease. RA is a systemic autoimmune condition characterized by synovial inflammation and progressive joint deformity, and has been associated with a two-

to six-fold increase in the risk of HL, acute myeloid leukaemia and NHL overall, especially of the subgroups DLBCL, lymphoplasmacytic lymphoma, and extranodal lymphoma.[6,27-30] A Swedish matched case-control study found the risk of lymphoma particularly elevated among those with severe RA. High inflammatory activity, rather than its treatment, may have been a major risk determinant.[31] We confirmed the association with the same lymphoma subgroups and also found an increased association with T-cell NHL. The association between RA and lung cancer is likely due to the shared etiological factors, e.g. smoking.[32]

Chronic inflammatory bowel diseases

For inflammatory bowel disease (IBD) prevalence rates in the general population vary between 0.7% and 1.2%,[21] which is 50% higher than the prevalence recorded in our study. The registration systems might differ, or cancer patients might really have a lower prevalence of IBD than the general population. The 1.5-fold elevated relative risk of colon cancer was reported in earlier studies,[33] IBD however did not show a significantly higher risk for NHL.[7,28] Yet the slightly higher risk of FL and DLBCL in our study is not confirmed by other studies.

Connective and vascular tissue diseases

In patients with systemic lupus erythematodus the relative risks for lymphoproliferative disease have been described to be two to six-fold for DLBCL and MZL.[7,27,28,30,34,35] Furthermore, personal history of systemic lupus erythematodus was strongly associated with an increased risk of Hodgkin lymphoma.[6,30,36] Personal and family histories of sarcoidosis were also independently associated with an elevated risk for Hodgkin lymphoma. The extremely elevated risk for Hodgkin lymphoma in the first (0-1 year) latency period indicates a certain degree of diagnostic overlap with sarcoidosis. However, the risk for Hodgkin lymphoma remained strongly elevated 2-4 years after the reported hospital discharge with sarcoidosis, pleading against misclassification.[6] In our study CTD includes sarcoïdosis (M. Besnier Boeck), Wegener's disease, periarteriitis nodosa, and systemic lupus erythematodus, and we were unable to distinguish between these disorders. This could explain why we found an association for T-cell NHL, in addition to DLBCL.

Ulcers of the stomach and duodenum

In the Dutch general population, the prevalence of ulcers of the stomach varied between 0.1% and 0.5% and between 0.2% and 1.2% for ulcers of the duodenum.[21]

Our study showed a higher risk of MZL and extranodal NHL, which could be explained by the higher risk for mucosa-associated lymphoid tissue (MALT) tumours at the sites of those ulcers, as well as for low-grade lymphomas.[37] Ulcers of the stomach and duodenum are most likely caused by Helicobacter pylori. The observed association between ulcers and lung cancer probably results from the deleterious effect of smoking on the gastric and duodenal mucosa.[38-40]

Hepatitis

Hepatitis B virus (HBV) was one of the first oncoviruses, detected by Blumberg in 1963.[22] Globally, approximately 2 billion people have been infected with HBV, and 350 million are chronically infected carriers of the virus. Hepatitis C virus (HCV) affects about 3% of the world's population, especially in Africa and Asia.[22] Chronic infections with HBV or HCV are known to be causally associated with a large amount of hepatocellular carcinoma.[41] Prevalence of HCV was higher among malignant lymphoma patients than among controls.[42-44] The association between HCV infection and B-cell NHL has been demonstrated, especially in highly endemic geographical areas.[44] Patients with B-cell NHL had a significantly higher rate of seropositivity for HBV antibodies (HBsAb) compared to a control group. However, patients in the T-NHL subgroup exhibited a seropositive rate of HBsAb similar to that of the control group.[45] We also showed this higher prevalence of hepatitis in haematological malignancies, especially for aggressive B-cell NHL.[43] The significantly higher risk for MZL and the lower risk for FL could not be confirmed in our study.[37,43]

HIV

Up to 10% of people with HIV will eventually develop non-Hodgkin lymphoma. Mechanisms for the carcinogenic potential of HIV are related to the dramatically compromised immune system.[22,46] Particularly lymphomas in extra nodal locations appear to be associated with HIV.[47] In our study the relationship between aggressive B-cell lymphoma (e.g. DLBCL and MCL) was also very prominent.

Tuberculosis

Tuberculosis is an important risk factor for lung cancer, persisting years after the onset of tuberculosis. This could reflect the effects of chronic pulmonary inflammation and scarring.[48] Another reason could be that both TBC and lung cancer are detected by X-thorax and early signs of lung cancer may have been misdiagnosed as TBC. Finally, shared etiological factors, e.g. smoking, could be the reason for the

association between TBC and lung cancer.[49] In the positive association with TBC and lymphoproliferative malignancies, diminished immune defence (as shared aetiology) could have played a role.

Finding an infectious cause of cancer is not easy due to the extended latency, multi-factorial nature of cancer, as well as the importance of interacting factors. Positive associations may also arise spuriously, because the virus is activated as a consequence rather than a cause of the preceding process of carcinogenesis, or because the virus acts as a marker for the causal agent. Furthermore, associations may be missed if an unsuitable serological marker is used or if the virus has disappeared from the genome or if the parasite is eliminated during carcinogenesis.

Knowledge of the risk of cancer, and which specific cancer subtype plays a role is important for finding a potential cause of these cancers and maybe in the future for surveillance or prevention possibilities. Infections may already be responsible for over 15% of all malignancies worldwide, but probably in a smaller proportion in the Netherlands.[22] The proportion of total cancer deaths attributable to infectious agents is estimated to be about 7 to 10%.[41] Following tobacco use, alcohol use and diet, infections as a group may be an important preventable cause of cancer.[22]

Another important point is the treatment and follow-up of patients with both haematological malignancies and autoimmune or chronic inflammatory disorders. Different treatment options, longer event-free survival and lower overall survival of patients with lymphoma associated with autoimmune or chronic inflammatory disorders have been demonstrated in earlier studies.[44,50] For example, splenic lymphoma with villous lymphocytes showed regression after treatment of the hepatitis C infection.[51] Therefore, specific treatment protocols might need to be adapted.

The cumulative risk for HL at age 75 in the Netherlands during 1989-1991 was 0.2% and 0.13% for males and females, respectively, and for NHL 1.2% and 0.8%.[52] Even when one multiplies this risk two- or 3 fold, the absolute risk for a haematological malignancy remains low, but enough to anticipate in case of certain signs or symptoms. One of these signs could be angioedema, which seems to be dominated by alterations in the control of B-cell proliferation and hyperactivation of the complement system.[53]

Our study used the prevalence of co-morbidity to investigate the relationship between autoimmune or chronic inflammatory disorders and newly diagnosed patients with haematological malignancies. This is a rather novel method [16] including all case subjects with a lymphoma diagnosis in a population-based registry. This results in a large number of patients, and therefore we could study the association between known autoimmune and chronic inflammatory disorders with different subgroups of haematological malignancies. But we did not classify the severity and status of the autoimmune and chronic inflammatory disorders and were not able to record the date of diagnosis of autoimmune and chronic inflammatory disorders. Therefore we could not exclude co-morbidities diagnosed shortly before diagnosis of the malignancies, which could have led to some misclassification. However, we compared with control groups of patients diagnosed with other cancers, in whom the same misclassification has taken place.

In conclusion, this study confirms the positive association between some autoimmune and chronic inflammatory disorders and lymphomas in a population-based cancer registry. It further explores the different effects per subgroup of lymphoproliferative malignancies. Especially the positive association between RA and most lymphomas, ulcers of stomach and duodenum and marginal zone lymphoma, hepatitis and diffuse large B-cell lymphoma, HIV and aggressive B-cell lymphoma, and TBC and mantle cell lymphoma stood out. All in all, this is a fairly new approach to confirm or develop hypothesis on etiological factors about cancers in a population-based cancer registry.

Acknowledgements

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Chapter 4

Validation of a prognostic index

4.1

Validation, revision and extension of the Follicular Lymphoma International Prognostic Index (FLIPI) in a population-based setting

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Abstract

Background

The aim of this study was to validate the Follicular Lymphoma International Prognostic Index (FLIPI) in a population-based cohort and to study the relevance of revision and extension of the FLIPI.

Patients and methods

Data of 353 unselected patients, 1993-2002, in the Eindhoven Cancer Registry, were collected. Follow-up was completed up to January 1st, 2006. Multiple imputations for missing covariates were used. Validity was assessed by comparing observed to predicted survival of the original model and of a revised model with other prognostic variables.

Results

The original FLIPI stratified our cohort into three different risk groups based on stage, Hb, LDH, nodal involvement, and age. The discrimination between risk groups was not as good as in the original cohort. A model including age in three categories (≤60/61-70/>70 years) and presence of cardiovascular disease (yes/no) resulted in a better prognostic index. The 5-year overall survival rates were 79%, 59%, 28% in the low, intermediate and high risk groups for the extended FLIPI compared to 81%, 66%, 47% for the original FLIPI, respectively.

Conclusions

The performance of the FLIPI was validated in a population-based setting, but could significantly be improved by a more refined coding of age and by including the presence of CVD.

Introduction

Follicular lymphoma (FL) is an indolent lymphoma and accounts for one third of non-Hodgkin lymphomas in adults. The prognosis for patients with FL is heterogeneous and treatment options vary from "watchful waiting" to high-dose chemotherapy.[1] A validated prognostic index would help in evaluating and choosing between the different treatment options. Patients with a poor prognosis should be considered for more aggressive and experimental therapies while on the contrary, those with a good prognosis, may benefit from "watchful waiting" or less toxic regimens.

Recently, a new clinical prognostic index has been proposed for FL: the Follicular Lymphoma International Prognostic Index (FLIPI).[1] This index is based on large series of patients and proposes three risk groups according to the probability of survival. The score was defined on a training series of 1795 patients with complete values for age, Ann Arbor stage, marrow involvement, haemoglobulin (Hb) level, number of nodal site areas, lymphocyte count and serum lactate dehydrogenase (LDH) level. The total cohort consisted of 4167 trial patients, but information from 2372 patients was discarded due to missing values. Excluding patients because of missing values can lead to bias and is statistically inefficient.[2] Nowadays, methods such as multiple imputation (MI) for handling of missing data have become more standard and software is more readily available.[2,3]

In the original report a five-variable model included the risk factors: age (>60), Ann Arbor stage (III-IV), Hb level (<12 g/dl), number of nodal site areas (>4) and serum LDH (elevated).[1] The FLIPI has been validated in some subgroups,[1,4-7] but needs further validation in a population-based setting where we see a broader selection of patients, such as more elderly patients and more patients with co-morbidity.[8] Co-morbidity, if serious enough, is an independent prognostic factor.[9-11] For unselected Dutch patients with indolent NHL, the proportion of those with co-morbid conditions was 39% for patients aged 60 or younger and 69% for those older than 60.[12] Therefore, it is important to consider extension of the FLIPI with co-morbidity as a risk factor. The aim of this study was to validate the FLIPI in a population-based cohort and to study the relevance of revision and extension of the FLIPI.

Patients and methods

Study population and data collection

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 10 general hospitals and two large radiotherapy institutes.[13] Trained registration clerks actively collect data on diagnosis, topography, histology, stage and information about initial treatment (delivered within six months from diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status.[14]

Since 1993 the Eindhoven Cancer Registry also registers the presence of serious co-morbidity with prognostic impact at the time of cancer diagnosis, using a slightly modified version of the widely used Charlson co-morbidity index.[9,15] Co-morbidity was defined as any disease that was present at the time of cancer diagnosis. Co-morbidities were registered as dichotomous variables (yes/no), according to the medical history of the patient, the use of relevant drugs and diagnostic work-up. Cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) are diseases with significant influence on survival.[12,16] These were analyzed separately for their impact on prognosis. CVD included myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft, peripheral arterial disease and cerebrovascular diseases.

All patients with FL newly diagnosed between 1993 and 2002 were included (N=369). Patients with lymphoma diagnosed at autopsy were not selected. There were also some lymphoma, not otherwise specified and B-cell lymphoma, not otherwise specified patients recorded in our registry. Therefore, the represented series might reflect a slight under registration, but we are quite confident that nearly all FL patients were selected.

Additional data (Hb level, number of nodal areas and serum LDH level) were gathered from the medical records. The prognostic index was calculated according to the original FLIPI,[1] using the variables age >60 years, advanced stage (III-IV), increased serum LDH, Hb level <12 g/dl and nodal involvement (>4 sites). Three risk groups were considered: score 0-1, low risk; score 2, intermediate-risk; and score ≥3, high-risk.[1]

Follow-up was completed up to January 1st, 2006, with vital status obtained from the municipal personal records. Survival time was defined as the time from diagnosis till death or the end of the study.

Statistical analysis

The influence of risk factors on overall survival (OS) was studied by Kaplan-Meier curves and log-rank tests in univariate analysis. For reasons of efficiency and to avoid potential bias, we imputed missing covariates using correlations between variables. We used a multiple imputation (MI) procedure where each missing value was imputed five times. Imputed values were drawn from the predictive distribution in an imputation model that included all risk factors and the survival outcome. The variation among the five imputations reflects the uncertainty with which the missing values can be predicted. MI resulted in five complete datasets, which were analyzed with standard complete data methods. The results were combined to produce overall estimates and standard errors that reflected missing data uncertainty.[2] All analyses were performed for both complete cases as well as for single and multiple imputations. Results are reported with multiple imputated data, except for the Kaplan-Meier analyses, which were based on the first of the five imputated data sets. MI was performed with the aregImpute function in the R software package (v 2.5.1).

Validation of the FLIPI started with a comparison of the hazard ratios (HRs) of the risk factors. We checked whether the coefficients in the Cox regression equation needed to be updated, based on likelihood ratio (LR) statistics.[17] Next, we considered extension of the model with COPD (yes/no), CVD (yes/no), B-symptoms (yes/no), number of co-morbidities (yes/no and no/one/more than one), and a combination of these variables.

We used the c-statistic to study discrimination, which reflected to the ability of the (extended) FLIPI to assign higher predicted risks to subjects who have died during the follow-up than to subjects who survived the whole follow-up period. We also calculated the explained variation by the covariates as $R^2 = 1 - \exp(-LR/n)$. We used a bootstrap resampling procedure to correct for statistical optimism in the estimated c-statistic. Modelling was repeated in 200 bootstrap samples, with model testing in the original sample, for each of the five imputed data sets.[18] The SAS computer package (version 8.2, SAS Institute Inc., Cary, North Carolina, USA, 1999) and the R computer package (version 2.5.1) were used for statistical analyses.

Table 1. Characteristics of the patients and results of the univariate analysis of prognostic factors in the original report about FLIPI[1] (shown in italics) and our population-based sample.

	Number of patients (%)		5-year OS		10-year OS		Log-rank test P value (difference between subgroups per study)	
Total	*4167 (100%)*	353 (100%)	*71*	68	*49*	51	-	-
Age ≤60	*2625 (63%)*	196 (56%)	*78*	78	*58*	63	*<10-4*	<0.0001
Age >60	*1542 (37%)*	157 (44%)	*58*	56	*32*	33		
Missing	*0*	0	-	-	-	-	-	-
Stage I-II	*916 (22%)*	142 (40%)	*83*	78	*64*	60	*<10-4*	0.0013
Stage III-IV	*3246 (78%)*	210 (60%)	*67*	62	*44*	45		
Missing	*5*	1	-	-	-	-	-	-
Hb ≥12 g/dl	*3127 (82%)*	292 (87%)	*75*	71	*52*	53	*<10-4*	<0.0001
Hb <12 g/dl	*686 (18%)*	44 (13%)	*51*	45	*35*	32		
Missing	*354*	17	-	76	-	55	-	-
LDH normal	*2026 (79%)*	219 (79%)	*77*	73	*54*	54	*<10-4*	0.0053
LDH high	*540 (21%)*	59 (21%)	*58*	54	*41*	39		
Missing	*1601*	75	-	67	-	50	-	-
Lymph nodes N≤4	*2159 (65%)*	233 (66%)	*77*	74	*55*	54	*<10-4*	0.013
Lymph nodes N>4	*1163 (35%)*	118 (34%)	*64*	58	*42*	43		
Missing	*845*	2	-	-	-	-	-	-
Women	*2042 (49%)*	177 (50%)	*73*	68	*51*	53	*0.0025*	0.89
Man	*2125 (51%)*	176 (50%)	*69*	69	*46*	47		
Missing	*0*	0	-	-	-	-	-	-
No B-symptoms	*3212 (81%)*	263 (81%)	*74*	74	*51*	55	*<10-4*	<0.0001
B-symptoms	*753 (19%)*	60 (19%)	*56*	48	*37*	37		
Missing	*202*	30	-	59	-	38	-	-
No spleen involvement	*2976 (78%)*	329 (98%)	*75*	69	*53*	50	*<10-4*	0.98
Spleen involved	*840 (22%)*	8 (2%)	*58*	63	*37*	-		
Missing	*351*	16	-	62	-	47	-	-
No co-morbidity	-	196 (60%)	-	76	-	59	-	<0.0001
1 co-morbid condition	-	87 (27%)	-	61	-	38		
>1 co-morbid conditions	-	45 (14%)	-	48	-	35		
Missing	-	25	-	78	-	55	-	-
No COPD	-	307 (94%)	-	69	-	51	-	0.084
COPD	-	21 (6%)	-	46	-	46		
Missing	-	25	-	78	-	55	-	-
No CVD	-	279 (85%)	-	71	-	56	-	<0.0001
CVD	-	49 (15%)	-	48	-	24		
Missing	-	25	-	78	-	55	-	-

Legend: OS = overall survival, Hb=haemoglobin level, LDH = serum lactate dehydrogenase, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease.

Results

From 1993 to 2002, 369 patients had been diagnosed with FL. Sixteen patients were excluded, because information could not be gathered. The characteristics of the original FLIPI study population,[1] and our 353 patients at diagnosis are compared in table 1.

Median follow up was 58 months, and 138 patients died. Overall survival (OS) of the FL patients was similar in both studies (49% vs. 51% 10-year survival rates). Age >60, advanced stage (III-IV), increased serum LDH, Hb level <12 g/dl, number of involved sites >4, and the presence of B-symptoms, co-morbidity and CVD were significantly associated with dismal OS in univariate analysis (Table 1).

For 77 patients, the FLIPI score could not be calculated, due to missing values. The most frequent missing variable was serum LDH level. The 276 FL patients with complete data were categorized as low (45%), intermediate (25%) and high risk (30%), according to the FLIPI score. With imputation these proportions changed towards 47%, 26%, and 27% for low, intermediate and high risk groups, respectively. The low risk group had a 5- and 10-year OS of 81% and 62%, respectively; the intermediate risk group had a 5- and 10-year OS of 66% and 48%, respectively; those in the high risk group had the worst OS: 47% and 34% (Table 2).

The FLIPI score discriminated less between the three risk groups in our population-based study as compared with the original cohort (c-statistic in our refitted model was 0.64). The c-statistic was somewhat higher for the refitted model with five risk factors (0.66, 95% confidence interval 0.62-0.71). The lower discrimination was in agreement with lower hazard ratios (HR) than in the original study (Table 2).

Table 2. Results of the original FLIPI report (N=1795)[1] (shown in italics) and of a refitted Cox regression model in our population-based sample (N=353).

Risk group	Number of patients		HR (95%CI)		5-year OS (95%CI)		10-year OS (95%CI)	
Low	*646*	166	*1*	1	*91 (89-93)*	81 (74-86)	*71 (66-76)*	62 (51-71)
Intermediate	*664*	91	*2.3 (1.9-2.8)*	1.6 (1.1-2.5)	*78 (75-81)*	66 (55-75)	*51 (46-56)*	48 (31-62)
High	*485*	96	*4.3 (3.5-5.3)*	3.1 (2.1-4.5)	*53 (48-58)*	47 (36-56)	*36 (31-41)*	34 (23-45)

Legend: HR = hazard ratio, CI = confidence interval, OS = overall survival.

Age >60 years had a significantly stronger coefficient than originally estimated, while the other FLIPI covariates had similar or slightly smaller effects. To correct for the underestimation of age in the original FLIPI we considered age in three categories (≤60/61-70/>70 years, Table 3). Fifty-one percent of the patients was younger than 60 (N=181), 29% was between 60 and 70 years (N=103), and 20 percent was older than 70 years (N=69).

Next we investigated whether extending the model could improve the prognostic index. The R^2 of the original FLIPI model in our data was 11.7%. A model which included stage (I-II/III-IV), Hb level (≥12/<12 g/dl), LDH level (normal/high), nodal involvement (≤4 sites/>4 sites), age in three categories (≤60/61-70/>70) and CVD (yes/no) resulted in a better R2 (18%). This model can be used with scores between 0 and 7 (Table 3).

Table 3. Effects of predictors for the original,[1] (shown in italics) refitted and extended FLIPI model.

	HR (95%CI) FLIPI original (N=1795)	HR (95%CI) FLIPI refitted (N=353)	HR (95%CI) FLIPI extended (N=353)	Score
Age >60	*2.4 (2.0-2.8)*	2.9 (2.0-4.1)	-	-
Ann Arbor stage III-IV	*2.0 (1.6-2.6)*	1.6 (1.0-2.5)	2.1 (1.3-3.4)	1
Hb <12 g/dl	*1.6 (1.3-1.9)*	1.7 (1.1-2.7)	1.8 (1.1-2.7)	1
LDH elevated	*1.5 (1.3-1.8)*	1.3 (0.9-2.0)	1.4 (0.9-2.1)	1
Number of nodal areas >4	*1.4 (1.2-1.6)*	1.4 (0.9-2.1)	1.2 (0.8-1.9)	1
Age 60-70	-	-	1.7 (1.1-2.7)	1
Age >70	-	-	4.4 (2.9-6.9)	2
CVD	-	-	1.9 (1.2-2.9)	1

Legend: The original FLIPI is the model and the data from the article of Solal-Celigny et al.[1]
The refitted model is original model and our population-based data.
The extended model is the model we created after validation, revision and extension.
HR = hazard ratio, CI = confidence interval, Hb = haemoglobin level, LDH = serum lactate dehydrogenase level, CVD = cardiovascular disease.

If we categorized patients with a score <3 as low-risk, the 5- and 10-year OS were 79% and 62% (Table 4). An intermediate risk group contains patients with a score of 3 (5- and 10-year OS, 59% and 34%), and patients with >3 risk factors could be categorized as high risk (5- and 10-year OS only 28% and 21%, respectively).

Table 4. Survival according to the extended FLIPI model with and without categorization in three prognostic groups.

Number of risk factors	Number of patients	5-year OS (95%CI)	10-year OS (95%CI)	5-year OS (95%CI)	10-year OS (95%CI)
0	60	89 (78-95)	77 (59-88)	79 (73-84)	62 (53-70)
1	67	83 (71-90)	64 (45-78)		
2	101	71 (60-79)	52 (37-64)		
3	76	59 (46-69)	34 (17-53)	59 (46-69)	34 (17-53)
4	29	44 (26-61)	32 (16-50)	28 (15-41)	21 (10-33)
5 + 6	15 + 5	5 (0-21)	-		

Legend: OS = overall survival, CI = confidence interval.

Internal validation with 200 bootstrap samples showed a c-statistic of 0.70 for the extended model and of 0.66 for the categorization in three risk groups. The extended model could better discriminate groups with different survival than the original FLIPI (Fig 1).

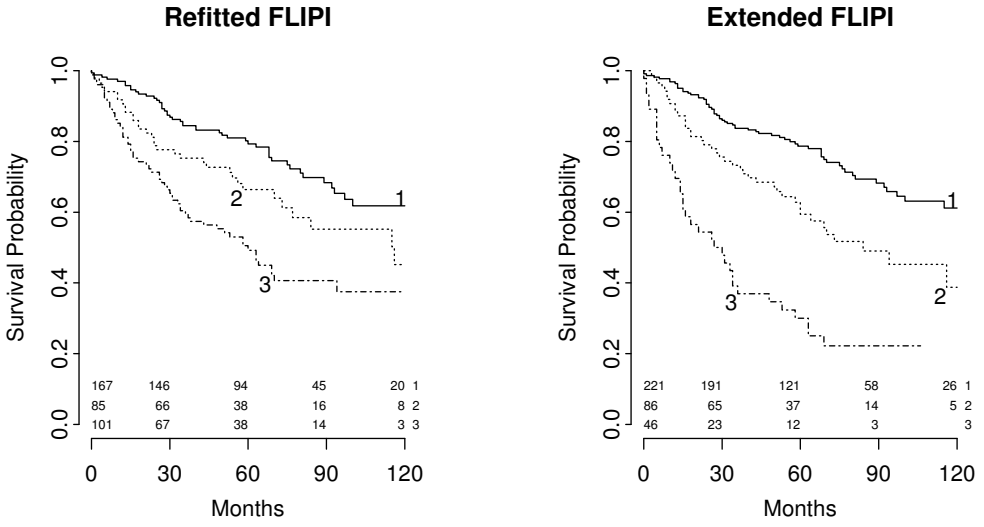

Figure 1. Kaplan Meier curve of refitted and extended FLIPI.

Legend: 1 = Low risk group, 2 = intermediate risk group, 3 = high risk group.
Numbers of patients, per subgroup and time period, are presented at the bottom of the figure.
Figure based on single imputation of missing covariates.

Discussion

Prognostic models should be valid for daily clinical practice allowing for stratification of patients and comparison of prognosis, and forming a basis for treatment decisions.[19] For our population-based setting, the FLIPI was reasonably valid, but could significantly be improved by a more refined coding of age (≤60/61-70/>70 years) and by including the presence of CVD as a risk factor.

For the validation we first examined the univariate relationship between possible prognostic factors and survival. A large tumour burden has long been recognized as an important adverse factor and can be estimated either directly considering stage or tumour diameter or indirectly by means of surrogate laboratory markers.[19] Also other clinical parameters have been correlated with prognosis including the number of nodal or extranodal sites, bone marrow involvement and the involvement of certain specific locations.[19] Similar results were found in our study: Ann Arbor stage and number of involved sites are important univariate prognostic factors. In several prognostic models, including this study, clinical and laboratory parameters, such as low Hb level, increased LDH level and B-symptoms are known as indirect parameters associated with the extent of the disease and/or its biological behaviour and have an independent poor prognostic value.[1,20-22]

The most important patient-related prognostic factor in FL was age, both in the univariate analyses as well as in our validation study, as widely reported in several studies.[20,22] With dichotomization, information of this continuous variable is lost.[23] Several age limits have been used to identify elderly patients with FL. Differently from aggressive lymphoma, an age limit of 70 years seems to better discriminate young versus elderly patients with FL.[24] In our study we used three age groups which resulted in a more discriminating prognostic model than the original model. We note that the age distribution was different between the original cohort and our cohort. Our study included more elderly patients (44% versus 37% older than 60 years). The most likely reason for the higher proportion of patients with advanced age in our population-based cohort is that the original report is based on data from clinical trials, with restrictive selection criteria. This may have led to a lower proportion of patients with advanced age and/or co-morbidity. CVD was related with age in our study, but the prognostic value of age was independent from the presence of co-morbidity and might reflect unknown co-morbid or pathophysiological conditions which are more frequent in elderly patients with subsequent less tolerance for treatment.

In several studies co-morbidity was found to be an independent prognostic factor for survival of non-Hodgkin lymphoma.[11,12] In our study several indicators of co-morbidity (number of co-morbid conditions, presence of CVD and COPD) were investigated as possible extensions for the prognostic model. Although the presence of co-morbidity was assessed from medical records, which is more clinically precise than self-reported or administrative databases, no information was available about the severity and duration of co-morbidity. If we missed co-morbidity in FL cases, they are likely to be less severe. In the univariate analyses the influence of co-morbidity on survival of FL was already visible. It remains to be debated whether poor prognosis associated with advanced age and presence of co-morbidity should be a reason for a different, more aggressive approach. This should preferably be investigated prospectively, studying which characteristics are important for treatment decisions. Studying cause-specific survival will also help to unravel this question.

Several studies have been performed to design prognostic models for patients with FL based on clinical and laboratory parameters, to identify patients in whom more aggressive experimental therapies are warranted. The FLIPI has recently been compared with other prognostic indices such as the International Prognostic Index (IPI) and the Italian Lymphoma Intergroup Index (ILI).[25] All three prognostic scores are easily applicable. In the comparison study the FLIPI score was able to classify more patients in the high-risk group than IPI and ILI. However, the high-risk group according to the ILI system identified a group with a particular worse prognosis as compared with IPI or FLIPI, suggesting ILI may have a relevant role in selecting patients with a very poor prognosis. Likewise our extended FLIPI should also be validated in other populations and compared with other prognostic indices.

Overall, currently available prognostic indices for FL, even if based on large series of patients, suffer from their retrospective nature. Missing values can be a problem, but should be handled with modern statistical approaches such as MI, to make retrospective analyses more reliable.[3] Prospective, complete data collection naturally remains preferable to retrospective analysis. Furthermore new predictors could not be included, because these variables were unknown or not tested in the past. For an example β_2-microglobuline, which was not investigated in our data and which has demonstrated to be a prognostic factor in FL patients.[26]

Another limitation is the fact that our study registered cases with FL before the advent of rituximab. In the Netherlands rituximab was introduced in 2003. Therefore, the follow-up for these patients was too short for validation, and this should be done in the future. In our study no detailed information about the first line treatment was available. Therefore, it could not be included in the validation of FLIPI. However, the influence of specific treatments on survival of FL was limited before the introduction of rituximab.

A feasible risk score ideally should have about the same proportion of patients in each risk group. This seems to be quite the case if the original FLIPI is used in the population-based cohort. Using the extended FLIPI, very few patients are in the high risk group, and the majority of patients are in the low risk group. However, we think that it is more important for a risk score that patients are discriminated clearly in prognosis than the fact that the proportion is almost equally distributed over the subgroups.

Despite these limitations, this extended FLIPI showed how important co-morbidity and age are in unselected patients with FL and therefore should be considered as an important factor for treatment decisions in FL patients in the general health care environment.

In conclusion, the extended FLIPI better prognosticates unselected FL patients by using a more refined coding of age and by including CVD. Therefore, we propose that the extended FLIPI can be considered for decision making on treatment in patients with FL, although we recognize that preferably prospective validation and further extension is required to better classify patients according to their prognosis, especially in this new era of treatment with rituximab.

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4.2

Validation, revision and extension of the Mantle cell lymphoma International Prognostic Index (MIPI) in a population-based setting

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Abstract

Background

The aim of this study was to validate the Mantle cell lymphoma International Prognostic Index (MIPI) in a population-based cohort and to study the relevance of revisions.

Patients and methods

We analyzed data of 178 unselected patients with stage III or IV mantle cell lymphoma, registered between 1994 and 2006, in the Eindhoven Cancer Registry. Follow-up was completed up to January 1st, 2008. Multiple imputations for missing covariates were used. Validity was assessed by comparing observed survival in our cohort to predicted survival of the original MIPI. A revised model was constructed with Cox regression analysis. Discrimination was assessed by a concordance statistic ('c').

Results

The original MIPI could stratify our cohort into three distinct risk groups based on ECOG, WBC count, LDH level, and age, with discrimination nearly as good as in the original cohort (c 0.65 vs. 0.63). A modified model including performance status in five categories (0/1/2/3/4) instead of two (0-1/2-4), the presence of B-symptoms (yes/no) and sex (male/female) in addition to the original variables resulted in a better prognostic index (c 0.75).

Conclusions

The MIPI is a valid tool for risk stratification, comparison of prognosis, and treatment decisions in an unselected Dutch population-based setting. Although the MIPI can significantly be improved, external validation on an independent data set is warranted before broad application of this modified tool can be recommended.

Introduction

Mantle cell lymphoma (MCL) is a relatively rare lymphoma entity accounting for approximately 3% to 6% of all non-Hodgkin lymphoma (NHL) cases. It has a poor prognosis with a reported median overall survival (OS) of only 30 to 43 months. Treatment results have been unsatisfactory, although a substantial variation in outcome was noted among individual cases with some patients achieving long lasting remissions.[1] A validated prognostic index would greatly help in developing new treatment strategies based on risk and prognosis, and for evaluating and choosing between different available treatment options.

Recently, a new clinical prognostic index has been proposed for MCL: the Mantle cell lymphoma International Prognostic Index (MIPI).[1] This index is based on data derived from 3 large randomized clinical trials and proposes 3 risk groups according to the probability of survival. The score was defined on 455 patients. Several candidate prognostic factors were included, but parts of these were excluded in multiple regression, because of a high number of missing values.

In the original MIPI, a 4-variable model included the risk factors performance status (ECOG), white blood cell (WBC) count, lactate dehydrogenase (LDH) level, and age.[1] However, the MIPI has not been validated yet. Validation is particularly important in a population-based setting to prove its use in a general health care environment containing more patients with advanced age and/or severe co-morbidity. Restrictive eligibility criteria, such as high age, serious co-morbidity, poor performance status and impairment of organ function, might have biased this trial based series.[2]

We previously found that co-morbid conditions were present in 48% of unselected patients with aggressive NHL under age 60, and even in 79% of those older than 60.[3] Co-morbidity, if serious enough, is an independent prognostic factor.[4-6] Moreover, we recently showed that the performance of the Follicular Lymphoma International Prognostic Index (FLIPI) could significantly be improved by a more refined coding of age and by including the presence of cardiovascular disease.[7] We therefore considered that also performance of the MIPI might be improved by adding others risk factors, amongst others co-morbidity. The aim of this study was to validate the original MIPI in a population-based cohort and to study possibilities for improvement of the MIPI.

Patients and methods

Study population and data collection

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.4 million inhabitants, 10 general hospitals and two large radiotherapy institutes.[8] Treatment decisions were generally made in multi-disciplinary meetings, within the frame work of the comprehensive cancer centre. Trained registration clerks actively collect data on diagnosis, topography, histology, stage and information about initial treatment (delivered within 6 months from diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status.[9] Data handling from our regional cancer registry was done according to the specifications of the officially recognised Code of Conduct Use of data in health research.

Since 1993 the Eindhoven Cancer Registry also registers the presence of serious co-morbidity with prognostic impact at the time of cancer diagnosis, using a slightly modified version of the widely used Charlson co-morbidity index.[4,10] Co-morbidity was defined as any other disease that was present at the time of cancer diagnosis. Co-morbidities were registered as dichotomous variables (yes/no), according to the medical history of the patient, the use of relevant drugs and diagnostic work-up. Cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) are diseases with significant influence on survival.[3,11] These were analyzed separately for their impact on prognosis. CVD included myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft, peripheral arterial disease and cerebrovascular diseases.

All patients with stage III and IV MCL newly diagnosed between 1994 and 2006 were included (N=181). Selection was based on WHO classification, documented from the medical records and registered in the cancer registry as ICD-O-3 morphology code 9673 and ICD-O-2 morphology code 9672, with the exclusion of tumours with localization in the stomach, bowel, lung, salivary glands, eye and skin. Patients with lymphoma diagnosed at autopsy were not selected. Additional data (performance status according to WHO criteria, LDH level, haemoglobin level, albumin level, β_2-microglobulin, Ki-67, chemotherapeutic regimen, platelets and WBC (lymphocyte, granulocyte and monocyte count)) were gathered from a new study of the medical records.

A prognostic index was calculated according to the original MIPI,[1] ($MIPI_{original/refitted}$ score = 0.03535*age (years) + 0.6978 (if ECOG >1) + 1.367*log10 LDH (ULN) + 0.9393*log10 WBC (10^6)). This score classifies patients with a total score smaller than 5.7 as low risk (LR), patients with a score of 5.7 to 6.2 as intermediate risk (IR) and patients with score higher than or equal to 6.2 as high risk (HR).[1]

Follow-up was completed up to January 1st, 2008, with vital status obtained from the municipal personal records. Survival time was defined as the time from diagnosis till death or the end of the study.

Statistical analysis

Missing values may occur selectively across patients. Exclusion of patients with missing values might bias the results. Therefore, we imputed missing covariates using correlations between variables. We used a multiple imputation (MI) procedure where each missing value was imputed 5 times. Imputed values were drawn from the predictive distribution in an imputation model that included all risk factors (age, LDH, total leukocyte and lymofcyte, granulocyte, trombocyte count, performance status, number of co-morbidities, cardiovascular disease, COPD, sex, spleen involvement, B-symptoms, stage, albumine and haemoglobine) and the survival outcome. Imputation of missing predictor values using the outcome is preferred over imputation without outcome and is no self-fulfilling prophecy.[12] The variation among the 5 imputations reflects the uncertainty with which the missing values can be predicted. Multiple imputations resulted in 5 completed datasets, which were analyzed with standard statistical methods. The results were combined to produce overall estimates and standard errors that reflected missing data uncertainty.[13] All analyses were performed for both complete cases as well as for single and multiple imputations. All results are reported with multiple imputed data, except for the Kaplan-Meier analyses, which were based on a single imputed data set. We checked the results of the randomly chosen single imputations, and those were comparable with the multiple imputation.

Validation of the MIPI started with a comparison of the hazard ratios (HRs) of the risk factors (refitted MIPI). We checked whether the coefficients in the Cox regression equation needed to be updated, based on likelihood ratio (LR) statistics,[14] and for the categorical variables if other cut points should be used (revised MIPI). Next,

we considered extension of the model with COPD (yes/no), CVD (yes/no), the number of co-morbidities (yes/no or no/one/more than one), and a combination of these variables. We calculated the explained variation by the covariates as $R^2 = 1 - \exp(-LR/n)$. Furthermore we evaluated if sex, the presence of B-symptoms, stage, chemotherapeutic regimen, transplantation, haemoglobin level, β_2-microglobulin level, albumin level and lymphocyte, granulocyte, monocyte and platelet count, and a combination of these variables could further improve the MIPI (modified MIPI). We used a stepwise approach, to include the variable who improved the model the most. Finally we tested the value of Ki-67 level, to validate the biological index of MIPI (MIPIb).

We used the c-statistic to study discrimination, which reflected to the ability of the (modified) MIPI to assign higher predicted risks to subjects who died during the follow-up than to subjects who survived during the follow-up period. We used a bootstrap resampling procedure to correct for statistical optimism in the c-statistic for the refitted and modified models. Modeling was repeated in 200 bootstrap samples, with model testing in the original sample.[15] Statistical analyses were performed using SAS software (version 9.1, SAS Institute Inc., Cary, North Carolina, USA, 1999), and R software (v 2.5.1, R Foundation for Statistical Computing, Vienna, Austria), with MI using the aregImpute function.

Results

Of the 181 stage III and IV MCL patients, three were excluded, because no sufficient information could be gathered. Our population-based study included more patients with advanced age and more patients with a lower performance status, as compared with the original MIPI study (Table 1). As seen in the original study, lymphocyte, granulocyte, monocyte counts, albumin and serum β_2-microglobulin had a high percentage of missing values. Furthermore it was difficult to gather data on performance status from the medical records in a quarter of the patients. Ki-67 was sporadically tested and for 78% information about this test was missing. For tumours that were tested on Ki-67, recording of the test result in the medical record varied from the exact percentage to a description of the results (for example positive or high). We tried to divide these results in 3 categories: low or < 10%, positive or 10%-29% and high or ≥30%.

In our study population 126 patients died, accounting for a 1 and 5-year survival rate of 80% and 34% respectively, resulting in a lower median overall survival (OS) than in the original study (26 vs. 57 months), with a median follow-up of the surviving patients of 47 vs. 32 months, respectively. For 60 patients the MIPI score could not be calculated, due to missing values. The 118 MCL patients with complete data were categorized as low (31%), intermediate (19%) and high risk (51%), according to the MIPI score. With multiple imputations these proportions changed towards 28%, 23%, and 49%, respectively. The low risk group had a 1- and 5-year OS of 88% and 54%; the intermediate risk group had 1- and 5-year OS of 83% and 41%; and those in the high risk group had the worst OS: 68% and 20%, respectively. In our cohort the MIPI score discriminated nearly as good as in the original cohort (c 0.65 vs. 0.63).

Table 1. Baseline patient characteristics

Parameter	*Original study* [1]	Current study	
Total number of patients	*455*	178	
Median age, years (range)	*60 (34-86)*	67 (40-89)	
Males (%)	*344 (76)*	124 (70)	
Missing (%)	*0 (0)*	0 (0)	
ECOG=0 (%)	*147 (33)*	70 (52)	
ECOG=1 (%)	*263 (58)*	34 (25)	
ECOG=2 (%)		20 (15)	
ECOG=3 (%)	*42 (9)*	5 (4)	30 (22)
ECOG=4 (%)		5 (4)	
Missing (%)	*3 (1)*	44 (25)	
Stage=4 (%)	*384 (84)*	141 (79)	
Missing (%)	*0 (0)*	0 (0)	
B-symptoms present (%)	*196 (43)*	62 (38)	
Missing (%)	*4(1)*	16 (9)	
Median WBC count, 10^9/L (range)	*7.9 (1.0-764)*	9.2 (1.4-360)	
Missing (%)	*4 (1)*	2 (1)	
Median lymphocyte count, 10^9/L (range)	*2.1 (0.35-625)*	13.7 (0.13-116)	
Missing (%)	*33 (7)*	19 (11)	
Median granulocyte count, 10^9/L (range)	*4.2 (0.19-26.4)*	4.0 (0.0-88)	
Missing (%)	*42 (9)*	84 (47)	

Parameter	*Original study (1)*	Current study
Median monocyte count, 10^9/L (range)	*0.5 (0.014-10.9)*	1.1 (0.0-40)
Missing (%)	*47 (10)*	28 (16)
Median platelet count, 10^9/L (range)	*188 (3-1346)*	178 (10-626)
Missing (%)	*3 (1)*	3 (2)
Median LDH, /ULN (range)	*0.86 (0.15-5.3)*	1.03 (0.09-25.5)
Missing (%)	*12 (3)*	18 (10)
Median Hb (males), g/L (range)	*133 (55-175)*	126 (59-168)
Median Hb (females), g/L (range)	*124 (30-149)*	120 (51-152)
Missing (%)	*2 (0.4)*	1 (1)
Median albumin, /ULN (range)	*0.8 (0.36-1.26)*	0.81 (0.34-1.08)
Missing (%)	*187 (41)*	48 (27)
Median β_2-micorglobulin, /ULN (range)	*1.1 (0.06-8)*	2.3 (0.6-4.6)
Missing (%)	*170 (37)*	119 (67)
Ki-67	*Median: 14.5%*	Low: 9 (23%)
	range: (1.2-91.0)	Positive: 13 (33%)
		High: 18 (45%)
Missing (%)	*219 (48)*	138 (78%)
No co-morbidity	-	73
1 co-morbid condition	-	44
>1 co-morbid conditions	-	51
Missing (%)	-	10 (6)
COPD (%)	-	17
CVD (%)	-	43
*Treatment	*CHOP: 255 (56%)*	CHOP (like): 76 (43%)
	RCHOP: 141 (31%)	R-CHOP: 27 (15%)
	MCP: 50 (11%)	Induction treatment for ASCT: 7 (4%)
	Other: 9 (2%)	Palliative CT: 34 (19%)
		None: 31 (18%)
Missing (%)	*0 (0)*	3 (2)

Legend: ECOG = Performance status, WBC = White blood cells, LDH = Serum lactate dehydrogenase level, Hb = Haemoglobin level, COPD = Chronic obstructive pulmonary disease, CVD = Cardiovascular disease.
*Treatment: CHOP (like) = CHOP, CATPBV, CAVMP/BV. Induction treatment for ASCT = CHOP+DHAP/VIM, RCHOP+ high dose Ara-C, high dose Ara-C. Palliative CT = CVP, Chloorambucil, VMP, CECP.

While the discrimination of the whole model was comparable, the hazard ratio (HR) of performance status was somewhat higher, and the HR's of LDH level and WBC count were a little lower than in the original study (Table 2). To correct for the underestimation of performance status in the original MIPI we considered to use the ECOG score in five categories in the revised model. Furthermore, we investigated whether extending the model could improve the prognostic index. The R^2 of the refitted MIPI model was 23%, with a LR of 47. A modified model which included also the presence of B-symptoms and sex resulted in a substantially and significantly ($p<0.001$) better R^2 (49%) and LR (121). Hb level, albumin level, number of co-morbidities and the presence of CVD were significant prognostic factors in univariate analyses (data not shown). However, at multivariable analysis the MIPI model could not be further improved by extension with COPD, CVD, number of co-morbidities, stage, treatment, transplantation, Hb level, albumin level, β_2-microglobulin level, lymphocyte, granulocyte, monocyte and platelet count (data not shown).

Table 2. Hazard ratios (HR) in the original, refitted, and modified MIPI models.

	HR (95%CI) MIPI original	HR (95%CI) MIPI refitted	HR (95%CI) MIPI modified
Age (1 year older)	*1.04 (1.02-1.06)*	1.04 (1.03-1.05)	1.05 (1.04-1.06)
ECOG (2-4 vs 0-1)	*2.01 (1.19-3.39)*	2.75 (2.21-3.42)	-
LDH (10-fold)	*3.92 (1.48-10.37)*	1.48 (1.08-2.03)	1.47 (1.08-2.00)
WBC count (10-fold)	*2.56 (1.66-3.95)*	1.97 (1.52-2.54)	1.23 (0.96-1.57)
ECOG (4 vs 3 vs 2 vs 1 vs 0)	-	-	1.77 (1.61-1.95)
B-symptoms (yes vs no)	-	-	2.22 (1.80-2.74)
Sex (male vs female)	-	-	2.19 (1.77-2.70)
*C statistic	*0.65*	0.63	0.75

Legend: The original MIPI is the model and the data from the article of Hoster et al.[1]
The refitted model is original MIPI model and our population-based data.
The modified model is the model we created after validation, revision and extension.
HR = Hazard ratio, 95%CI = 95% Confidence interval, ECOG = Performance status, LDH = Serum lactate dehydrogenase level, WBC = White blood cell.
*C statistic is corrected for optimism with bootstrapping, after dividing into three subgroups.

The modified model can be calculated by: $MIPI_{modified\ score}$ = 0.0453*age (years) + 0.5706*ECOG (subgroup) + 0.3854*log10 LDH (ULN) + 0.2035*log10 WBC (10^6) + 0.7994 (if B-symptoms were present) + 0.7820 (if sex was man). Three subgroups

were defined with the cut off points 4.65 and 5.90, leading to some loss in prognostic performance (R2 43% and LR 100). Potential cut points were assessed as in the original study, to find the best discrimination between groups.[1] The low risk group contained 64 (36%) patients; for the intermediate risk group this was 75 (42%) and 39 (22%) for the high risk group. The median survival times were 90, 29, and 6 months in the low, intermediate and high risk groups for the modified MIPI compared to >90, 51, and 29 months for the original MIPI respectively. This resulted in a 1- and 5-year OS of 95% and 66%, for the low risk group; the intermediate risk group had 1- and 5-year OS of 81% and 24%; those in the high risk group had the worst OS: 38% and 0%, respectively. The modified model could better discriminate groups with different survival than the original MIPI (Figure 1).

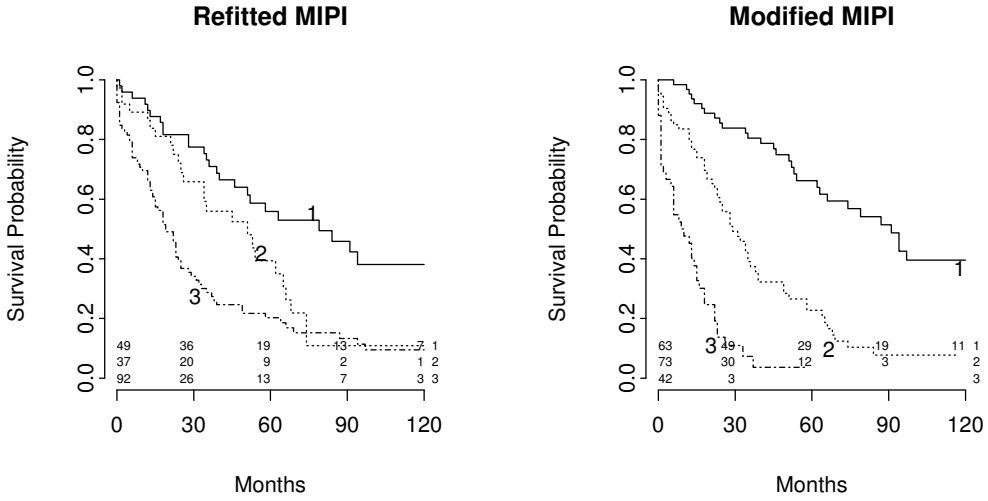

Figure 1: Kaplan Meier curve of refitted and modified MIPO

Legend: 1 = Low risk group, 2 = intermediate risk group, 3 = high risk group.
Numbers of patients, per subgroup and time period, are presented at the bottom of the figure
Figure based on single imputation of missing covariates.

With regards to the biological index (MIPIb), we tried to collect data on the proliferation marker Ki-67, but this marker was not tested or poorly recorded in the medical records. For those cases with an available test on Ki-67 the positivity did not contribute to the MIPI, when divided into four categories. No improvement in the MIPI was noted after MI of the missing Ki-67 values.

Discussion

Prognostic models should be valid for daily clinical practice, allowing risk stratification and comparison of prognosis, and thus forming a rationale for treatment decisions. Validation in population-based settings is important because it shows if a prognostic index is functional in daily practice. In our population-based setting the MIPI was valid, but the MIPI could significantly be improved by a more refined coding of performance status and by including the presence of B-symptoms and sex as risk factors.

The most likely reason for the higher proportion of patients with advanced age in our population-based cohort is that the original report was based on data from clinical trials, with restrictive selection criteria. For instance the European MCL trial[16] had an age limit up to 65 years. Furthermore all three trials,[16-18] which formed the basis for the original study, excluded patients with serious concomitant diseases, poor performance status, or significant impairment of organ function.[1] We found the prognostic value of age to be independent from the presence of co-morbidity and performance status and therefore might reflect unknown co-morbid or pathophysiological conditions more frequently encountered in elderly patients with subsequent less tolerance for treatment.

In several studies co-morbidity was found to be an independent prognostic factor for survival in NHL patients.[3,6] Although the presence of co-morbidity in general, and cardiovascular disease in particular, were significant prognostic factors in univariate analyses, these factors could not improve the prognostic performance of MIPI model. This is probably explained by the fact that performance status was included in the model, and this factor partly reflects the presence of co-morbidity.[19] The higher proportion of patients with a poorer performance status in our study could also be the reason for the relatively low impact of performance status in the original model containing only very few patients with a poor performance status. It remains to be debated whether the poor prognosis associated with advanced age and poorer performance status should be a reason for a different, more aggressive treatment approach, because previous studies have shown that these patients experience more side effects of treatment.[20] This should preferably be investigated prospectively. Furthermore, studying cause-specific survival may also help to unravel this question, since part of the worse prognosis might also be due to mortality from the co-morbidity itself. The above mentioned factors could also be the explanation for

the lower median survival in our study compared to the original study.[1] Of note, other population-based studies showed a similar survival to our study.[21,22]

The prognostic effect of sex was not observed in the original study.[1] The incidence of MCL is known to be higher in males.[1,21,23] Although the prognostic effect of sex is not found in other studies,[1,3,21,24] it did improve the MIPI significantly in our study. In diffuse large B-cell lymphoma the prognostic effect of sex was found after the introduction of rituximab.[25] In this study only 4% of the patients was treated with rituximab We therefore think that this does not explain the prognostic effect of sex. Since we cannot provide a good explanation for this effect, it is important to validate the modified MIPI, with sex as covariate, in other populations. Another interesting observation in our study is that the presence of B-symptoms had an important prognostic effect and could improve the MIPI. This effect has also been reported in univariate analyses in some earlier studies,[1,26] but disappeared in multivariable analyses, in contrast to other studies which have shown that it was an important independent risk factor, also in multivariable analyses.[21,27]

In our study the prognostic effect of the biological marker Ki-67 could not be tested reliably, because of a very high percentage of missing values and no specific coding in the medical records. The original study also showed a high percentage (48%) of missing values. Since recent studies report Ki-67 to be an important prognostic factor for mantle cell lymphoma patients,[24,26,28-30] it is important that the prognostic significance of Ki-67 in the MIPI model should be investigated.

The current analyses did not include patients with limited stage I or II MCL, because the MIPI was not designed for these patients. Hoster et al.[1] stated that the prognostic relevance of stage was not consistently seen in the literature. Moreover, the proportion of patients with stages I or II is rather low in MCL and they require a different therapeutic approach. Thus Hoster et al. limited their investigation to the advanced stage MCL patients with standardized treatment options (56% CHOP, 31% R-CHOP and 11% MCP).[16-18] This original data was also limited to patients who should tolerate moderately intensive chemotherapy. In our study the proportion of unselected patients receiving moderately intensive treatment was obviously lower, as compared to trial-based studies, as the original publication. More patients were treated with relatively mild regimens (43% CHOP (like), 15% RCHOP, 4% induction

treatment for ASCT, 19% palliative chemotherapy and 18% no chemotherapy). Treatment decisions are probably correlated with prognostic factors in our retrospective study. When we included treatment in our multivariable analyses, no additional prognostic value of treatment could be detected as compared with the other factors of MIPI, and therefore we can conclude that the other prognostic factors are more important for this patient population.

Several candidate prognostic factors were included in the original study,[1] but part of these were excluded in multiple regression, because of a high number of missing values. It is now widely recognized that complete case analyses with missing values in the data set can lead to bias of the results and are statistically inefficient.[13] Nowadays, application of methods for handling missing data is becoming more standard and software is more readily available. Multiple imputation is considered a sound statistical methodology for handling complex missing data problems,[13,31] that contributes to statistically more reliable retrospective analyses, including ours.

In conclusion, the MIPI is a valid tool for risk stratification, comparison of prognosis, and treatment decisions in an unselected Dutch population-based setting. Although the MIPI can significantly be improved, external validation on an independent data set is warranted before broad application of this modified tool can be recommended.

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Chapter 5

Elderly

5.1

Less standard therapy and poorer survival for senior patients with aggressive B-cell non-Hodgkin lymphoma diagnosed 1997-2007, in the Netherlands

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To be submitted

Abstract

Background

We investigated the deviation from standard therapy for senior patients with non-Hodgkin lymphoma (NHL) and its impact on overall survival.

Patients and methods

Data of all 11,659 patients, aged 45 years and older, with aggressive B-cell NHL, recorded in the Netherlands Cancer Registry, and newly diagnosed between 1997 and 2007, were used and follow-up was completed until January 1st, 2009.

Results

Of the 11,659 patients with NHL, 1842 were aged 75-79 years, 1361 80-84 years and 912 85 years and older. Only 24% of 1077 patients with stage I, older than 75 years, received the standard combination of chemotherapy (CT) and radiotherapy (RT), versus 46% of patients aged 45-74 years. Furthermore, 65% and 89%, respectively for patients with advanced disease (stage II-IV) who received CT as standard primary treatment. As expected, increasing age was strongly associated with lower adherence to treatment guidelines ($p<0.0001$) and also with overall survival. Overall survival remained significantly worse for patients not treated according to standard therapy, after adjustment for age. Interestingly, survival for patients with stage II-IV disease has significantly improved since 2002.

Conclusions

If therapies in older patients with aggressive B-cell NHL deviate so much from the standard, new policies should be developed for this growing group. Because chronological age is not the only criteria for justifying or denying access to a potentially curative therapy, balancing risk and benefits must be tailored to the condition of the individual patient.

Introduction

The number of elderly, and especially very elderly, with cancer is increasing considerably in most industrialised countries. In the Netherlands the number of elderly patients (aged 65 or older) diagnosed with cancer has increased from about 15,500 in 1990 to about 20,000 in 2000, and this number is expected to be over 26,000 in 2010. This means an increase of almost 50% in 20 years.[1] Management of cancer in this age group is often complicated by serious co-morbidity, interactions between drugs, reduced functional reserves, and cognitive impairment,[2-4] resulting in the use of substandard doses and regimens or even refraining from treatment, also by frequent refusal of the offered treatment, for example because they fear toxicity.[5,6]

For patients with advanced stage aggressive B-cell non-Hodgkin lymphoma (NHL), multi agent (CHOP-like) chemotherapy has been the first choice of treatment since 1995.[7] In the recent decade rituximab has been added to the standard treatment.[8] However, older patients with aggressive NHL received chemotherapy less frequently and dose intensity and the number of applied cycles has been described to be lower compared to younger patients.[9-12] Serious co-morbidity and poor performance status both negatively influenced adherence to standard treatment in older patients.[11] Although for patients with stage I disease a combination of chemotherapy and radiotherapy is recommended, radiotherapy is administered less frequently in the elderly without convincing evidence of less tolerance in elderly.[13,14]

Since elderly are often not or only selectively included in clinical trials,[15-18] evidence-based guidelines can hardly be based on these data. Studies with data from population-based cancer registries can give insight into patterns of treatment and outcome of unselected elderly cancer patients in everyday clinical practice.

The aim of this study was to investigate to which extent unselected senior patients with NHL received standard therapy and to determine the influence of sex, age, region, period of diagnosis and treatment on survival of these patients.

Patients and methods

Study population and data collection

Population-based data from all 8 regional Dutch cancer registries was used. These registries record data on patients newly diagnosed with cancer in all hospitals in the Netherlands (coverage at least 95% of Dutch population (16.3 million)).[19] Trained registrars routinely collect data on patient and tumour characteristics, like histology, tumour grade, localisation, morphology, and Ann Arbor stage directly from the medical records. Furthermore, primary treatment (first six months) was registered as dichotomous variables (yes/no) for chemotherapy (CT) and radiotherapy (RT).

All patients, aged 45 years and older, diagnosed with aggressive B-cell NHL between 1997 and 2007 were included (N=13,381). Aggressive B-cell NHL was classified according the WHO classification.[20]

Follow-up was completed until January 1st, 2009. In addition to follow-up by hospital records, this information was also obtained from the Municipal Personal Records Database (GBA). This institution collects data on vital status of all Dutch citizens. Survival time was defined as the time from diagnosis to death or the end of the study. Patients who were alive at the end of the study were censored at January 1st, 2009.

Statistical analysis

Because of the different treatment strategies, analyses were stratified, according to stage (I versus II-IV). Treatment was described, according to age group (45-64, 65-69, 70-74, 75-80, 80-84, 85+). The proportion of patients treated according to the investigated standard therapy was calculated. Since recommendations for treatment may have varied between regions in the Netherlands, and also may have changed during the investigated period, we included period of diagnosis and region in our multivariable analyses.

Crude survival rates were computed. The independent effects of stage, age and treatment on survival was analyzed with Kaplan-Meier curves and Cox regression analysis. Multivariable survival analyses were performed to estimate the hazard ratio of dying for the variables age, treatment, sex, stage, region, and incidence year.

Statistical analyses were performed using SAS software (version 9.1, SAS Institute Inc., Cary, North Carolina, USA, 1999).

Results

Of all 11,659 NHL patients, 4096 were aged 45-64, 1612 65-69, 1836 70-74, 1842 75-79, 1361 80-84, and 912 were 85 years and older. The stage distribution was: I: 26%, II: 19%, III: 17%, IV: 33% and unknown in 6%. The percentage of patients with unknown stage increased slightly with increasing age (table 1). Furthermore, in recent time periods the percentage of patients with advanced stage disease increased, and with unknown stage decreased. Eighty-one percent of the patients had diffuse large B-cell lymphoma, 12% mantle cell lymphoma, 5% follicular lymphoma grade 3, and 2% Burkitt lymphoma.

Table 1: Characteristics of newly diagnosed patients with aggressive B-cell NHL, between 1997 and 2007 in the Netherlands, by stage

		Stage I		Stage II-IV		Stage x	
		N	%	N	%	N	%
Age (years)	45-64	1076	26	2876	70	144	4
	65-69	412	26	1130	70	70	4
	70-74	420	23	1299	71	117	6
	75-79	463	25	1264	69	115	6
	80-84	347	26	893	66	121	9
	85+	267	29	504	55	141	15
Sex	Men	1573	25	4453	70	366	6
	Women	1412	27	3513	67	342	6
Incidence year	1997	262	30	545	62	73	8
	1998	241	28	528	61	94	11
	1999	275	31	552	62	58	7
	2000	252	27	640	68	56	6
	2001	286	28	688	67	51	5
	2002	247	24	714	69	73	7
	2003	253	23	763	70	67	6
	2004	297	26	800	70	51	4
	2005	310	25	873	70	65	5
	2006	283	23	899	73	54	4
	2007	279	21	964	74	66	5

		Stage I		Stage II-IV		Stage x	
		N	%	N	%	N	%
Region	1	510	23	1602	72	102	5
	2	351	26	893	67	86	6
	3	257	27	624	66	62	7
	4	669	27	1603	65	195	8
	5	224	22	728	71	71	7
	6	442	26	1170	70	64	4
	7	359	27	889	68	58	4
	8	164	24	449	66	69	10

Legend: N = number of patients

Of NHL patients with stage I, only 24% of those older than 75 years received the advised treatment with combined chemotherapy (CT) and radiotherapy (RT), compared to 46% of patients aged 45-74. This proportion declined with increasing age within age group 75+: 34% for patients aged 75-79, 26% in age group 80-84 and only 6% for those aged 85+, respectively (figure 1). A total of 271 elderly patients (75+) received CT alone (25%), which also declined with increasing age; 32% in age group 75-79 years, 24% and 15% in age groups 80-84 years and 85+ years, respectively. For patients with advanced stage (stage II-IV), 65% of patients aged 75 years and older received CT, compared with 89% in patients aged 45-74 years. This proportion decreased from 76% in age group 75-79 years to 63% and 40% in age groups 80-84 years and 85+ years, respectively (figure 1). In multivariable analyses increase of age was strongly and independently associated with lower adherence to standard therapy ($p<0.0001$) (table 2).

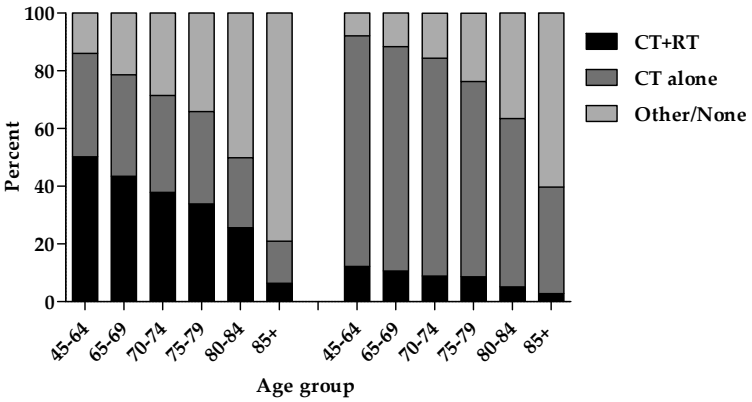


Figure 1: Treatment variation in patients with aggressive B-cell NHL, diagnosed between 1997 and 2007 in the Netherlands, by age and stage

Legend: RT = radiotherapy, CT = chemotherapy

Table 2: Odds ratios of increasing age on receiving standard therapy, by patients with aggressive B-cell NHL, diagnosed between 1997 and 2007 in the Netherlands, by stage

Stage	Age (yrs)	OR uni	95% CI	OR multi	95% CI
I	45-64	1	-	1	-
	65-69	0.8	0.6-0.96	0.7	0.6-0.9
	70-74	0.6	0.5-0.8	0.6	0.5-0.8
	75-79	0.5	0.4-0.6	0.5	0.4-0.6
	80-84	0.3	0.3-0.4	0.3	0.2-0.4
	85+	0.07	0.04-0.1	0.06	0.04-0.1
II-IV	45-64	1	-	1	-
	65-69	0.7	0.5-0.8	0.7	0.5-0.8
	70-74	0.5	0.4-0.6	0.5	0.4-0.6
	75-79	0.3	0.2-0.3	0.3	0.2-0.3
	80-84	0.1	0.1-0.2	0.1	0.1-0.2
	85+	0.06	0.05-0.07	0.05	0.04-0.06

Legend: OR uni = odds ratio univariate, 95% CI = 95% confidence interval, OR multi = odds ratio multivariable

Standard therapy for stage I patients was chemotherapy + radiotherapy and for stage II-IV chemotherapy

Multivariable OR was adjusted for incidence year, sex and region. For stage II-IV, adjustment was also made for stage (II vs. III vs. IV)

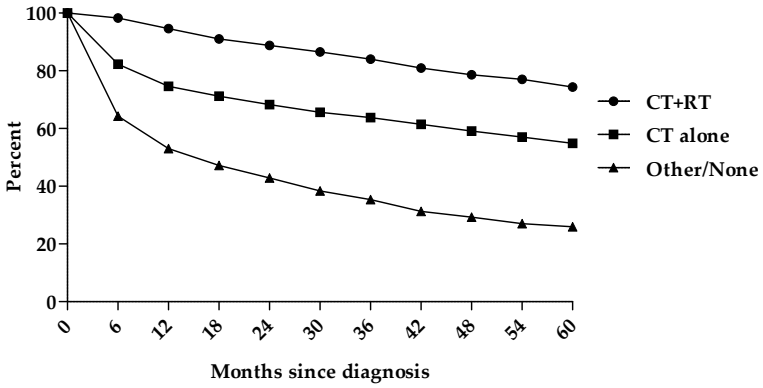
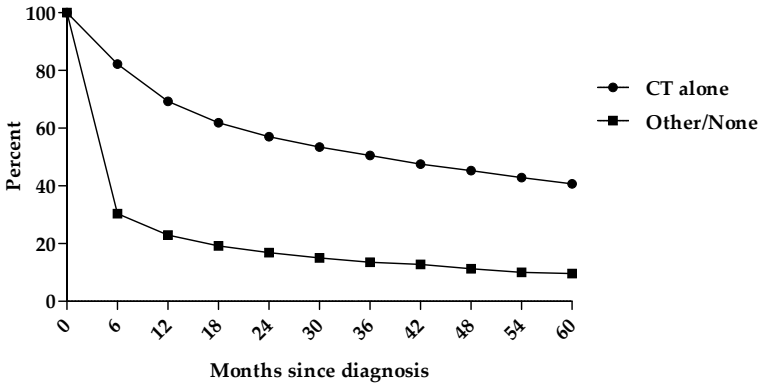


Figure 2: Overall survival of patients with aggressive B-cell NHL, diagnosed between 1997 and 2007 in the Netherlands, by treatment
A: Stage I

Legend: CT and RT is the standard treatment
P-value logranktest=<0.0001



B: Stage II-IV

Legend: CT is the standard treatment
P value logranktest=<0.0001
RT = radiotherapy, CT = chemotherapy

Overall 5-year survival for stage I patients was 53%, ranging from 67% for patients aged 45-74 years to 44% for patients aged 75-79, 26% for those aged 80-84 and 9% for patients aged 85+. For advanced stage patients overall 5-year survival was 35%, ranging from 44% for patients aged 45-74 years to 24% for patients aged 75-79, 13% for those aged 80-84 and 6% for patients aged 85+. Not receiving standard therapy was independently associated with reduced overall survival, which was found in both stage groups. (figure 2 and table 3). Among NHL patients with advanced stage

male sex and high stage were also independent dismal prognostic factors for overall survival. Furthermore, for patients with advanced stage NHL overall survival has significantly improved since 2002, this pattern was visible for both patients younger and older than 75. Region of diagnosis did not influence overall survival.

Table 3: Univariate and multivariable survival analyses of patients with aggressive B-cell NHL, diagnosed between 1997 and 2007 in the Netherlands, by stage

			HR uni	95%CI	HR multi	95%CI
Stage I	Age (yrs)	45-64	1.0	-	1.0	-
		65-69	1.7	1.4-2.1	1.6	1.4-2.0
		70-74	2.3	1.9-2.7	2.1	1.7-2.5
		75-79	2.9	2.5-3.4	2.5	2.1-3.0
		80-84	4.6	3.9-5.4	3.4	2.9-4.1
		85+	6.7	5.7-8.0	4.0	3.3-4.8
	Treatment	RT+CT	1.0	-	1.0	-
		CT alone	1.9	1.7-2.2	2.0	1.7-2.3
		Other/None	4.4	3.9-5.0	3.1	2.6-3.5
	Sex	Female	1.0	-	1.0	-
		Male	0.9	0.8-1.0	1.1	0.9-1.4
	Region	1	1.0	-	1.0	-
		2	0.9	0.8-1.2	1.1	0.9-1.4
		3	1.0	0.8-1.3	1.0	0.8-1.3
		4	1.0	0.8-1.1	1.0	0.9-1.2
		5	0.9	0.7-1.1	1.0	0.8-1.2
		6	1.1	0.9-1.3	1.1	0.9-1.3
		7	1.0	0.8-1.2	1.0	0.9-1.3
		8	0.9	0.7-1.1	0.9	0.7-1.2
	Incidence year	1997	1.0	-	1.0	-
		1998	1.0	0.8-1.2	0.9	0.8-1.2
		1999	1.0	0.8-1.3	1.0	0.8-1.3
		2000	1.2	0.9-1.4	1.2	1.0-1.5
		2001	0.9	0.7-1.2	1.0	0.8-1.3
		2002	1.0	0.8-1.3	1.0	0.8-1.2
		2003	1.0	0.8-1.3	1.1	0.9-1.4
		2004	0.9	0.7-1.1	1.0	0.8-1.3
		2005	1.0	0.8-1.2	0.9	0.7-1.2
		2006	0.9	0.7-1.2	1.0	0.7-1.3
		2007	0.9	0.7-1.2	0.9	0.7-1.2

			HR uni	95%CI	HR multi	95%CI
Stage II-IV	Age (yrs)	45-64	1.0	-	1.0	-
		65-69	1.4	1.3-1.6	1.4	1.3-1.5
		70-74	1.7	1.6-1.9	1.7	1.6-1.8
		75-79	2.3	2.2-2.5	2.2	2.0-2.4
		80-84	3.1	2.8-3.4	2.7	2.5-3.0
		85+	4.3	3.8-4.7	3.0	2.7-3.4
	Treatment	CT	1.0	-	1.0	-
		Other/None	3.5	3.3-3.7	2.6	2.4-2.8
	Sex	Female	1.0	-	1.0	-
		Male	1.0	1.0-1.1	1.2	1.1-1.2
	Region	1	1.0	-	1.0	-
		2	0.9	0.8-1.0	0.9	0.8-1.0
		3	0.9	0.8-1.0	0.9	0.8-1.0
		4	0.9	0.9-1.0	1.0	0.9-1.0
		5	1.0	0.9-1.1	1.0	0.9-1.1
		6	1.0	0.9-1.1	1.0	0.9-1.1
		7	1.0	0.9-1.1	0.9	0.9-1.1
		8	1.0	0.9-1.2	1.1	1.0-1.3
	Incidence year	1997	1.0	-	1.0	-
		1998	1.1	1.0-1.3	1.0	0.9-1.1
		1999	1.0	0.8-1.1	0.9	0.8-1.0
		2000	1.0	0.9-1.1	1.0	0.8-1.1
		2001	1.0	0.9-1.1	0.9	0.8-1.1
		2002	0.9	0.8-1.0	0.9	0.8-1.0
		2003	0.9	0.8-1.1	0.9	0.8-1.0
		2004	0.8	0.7-0.9	0.7	0.6-0.8
		2005	0.7	0.6-0.8	0.7	0.6-0.7
		2006	0.7	0.6-0.8	0.7	0.6-0.8
		2007	0.7	0.6-0.8	0.6	0.6-0.7
	Stage	II	1.0	-	1.0	-
		III	1.3	1.2-1.4	1.4	1.3-1.6
		IV	1.6	1.5-1.7	1.7	1.6-1.8

Legend: HR uni = hazard ratio univariate, 95% CI = 95% confidence interval, HR multi = hazard ratio multivariable, RT = radiotherapy, CT = chemotherapy

Discussion

Of the elderly (75+) NHL patients with stage I only 24% received standard therapy whereas for elderly patients with advanced stage (stage II-IV) this was 65%. In multivariable analyses increasing age was strongly associated with lower adherence to standard therapy. In both stage groups not receiving standard therapy and high age were independently associated with poorer survival. For patients with stage II-IV aggressive NHL survival has improved since 2002.

Several clinical trials indicated that CHOP-like chemotherapy (since 2001 combined with rituximab) results in better survival, also in elderly patients.[7,8] However, these trials have included only relatively healthy elderly. Our study has shown that in everyday clinical practice elderly received chemotherapy less often, which is in line with previous population-based studies.[9,10,12] Refraining from therapy in the elderly is probably the result of serious co-morbidity, reduced functional reserves, cognitive impairment, interactions between drugs or reluctance of patients to accept chemotherapy.[2-4,6,10,12,21] Unfortunately, these characteristics are not routinely recorded in cancer registries and therefore we cannot give the exact explanation for the declined adherence to standard therapy.[6]

In our study age and treatment were important and independent determinants of overall survival. The negative influence of increasing age on overall survival might be due to an increased risk of death due to co-morbid conditions, being contra-indications for cytotoxic treatment, and/or exhibiting a higher rate of treatment-related complications, but more dose reductions and less intensive treatment of the co-morbid condition might also play a role. In all previous studies, increasing age was negatively related with overall survival for patients with aggressive NHL.[3,9,10,22,23] In our study treatment was not fully responsible for the difference in survival between elderly and younger patients, suggesting a role for other above mentioned factors. However, we had no information on type of chemotherapy and dose intensity. Furthermore, the following other well described patient-related variables may have played an important prognostic role: performance status, body-mass index, haemoglobin level, serum lactate dehydrogenase level, and treatment toxicity.[9,12,22,24-27]

The improved survival in the recent period for patients with advanced stage was probably caused by the increased use of more effective drugs, such as the anti-CD20 monoclonal antibody rituximab.[8,28] Furthermore, improved survival is most likely due to the use of more accurate diagnostics and better supportive care (haematological growth factors and prophylactic antibiotics) and prognostic tools might have been more often used.[29]

Some limitations of our study require careful consideration. First of all, details regarding the chemotherapeutical regimen and dose adherence are lacking. This limits elucidation of the differences in treatment and survival. In addition, the retrospective nature of our study has resulted in selection bias of relatively fit patients for standard treatment. Next to that, the use of monoclonal antibodies was not yet registered adequately in the national cancer registries. Furthermore, geriatric assessments and performance status had not been routinely scored nor recorded and co-morbidity in just one CCC.[12,30]

The strength of this study is that all Dutch patients with aggressive B-cell NHL are included. We therefore could document treatment and survival of a large series of unselected elderly patients giving insight in everyday clinical practice, with a relevant cohort of 912 patients aged 85 years or older.

In conclusion, only 24% of senior patients with stage I and 64% with advanced stage aggressive B-cell NHL were treated according the national guidelines. If therapies in older patients with aggressive B-cell NHL deviate so much from the standard, new policies should be developed for this growing group. Because chronological age is not the only criteria for justifying or denying access to a potentially curative therapy, balancing risk and benefits must be tailored to the condition of the individual patient.

Acknowledgments
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5.2

Two sides of the medallion: poor treatment tolerance, but better survival by chemotherapy in elderly patients with advanced stage aggressive B-cell non-Hodgkin lymphoma

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Abstract

Background

Twenty-nine percent of all newly diagnosed NHL patients in the Netherlands are ≥75 years. We investigated treatment for unselected elderly patients with advanced stage aggressive non-Hodgkin lymphoma (NHL) and its subsequent impact on treatment tolerance, response and survival.

Patients and methods

Data from all 515 advanced stage aggressive B-cell NHL patients, aged 75 or older, newly diagnosed between 1997 and 2004, were included from 5 regional population-based cancer registries in the Netherlands, covering 38 community hospitals and 3 university hospitals. Subsequent data on co-morbidity, performance status, detailed information on treatment, motives for adaptations or refraining from chemotherapy, and toxicities was collected from the medical records. Follow-up was completed until January 1st, 2009.

Results

Only 45% of patients received the standard therapy (CHOP-like chemotherapy). Motives for withholding chemotherapy were refusal by patient/family, poor performance status or estimated short life-expectancy. Of all patients receiving CHOP-like chemotherapy only 59% could complete at least 6 cycles. Grade 3 or 4 toxicity occurred in 68% of patients receiving CHOP-like therapy, but also in 40% of those receiving milder regimens. Complete remission was achieved in 64% of patients receiving at least 6 cycles of CHOP-like chemotherapy, but 43% of these had a recurrence. The independent effect of therapy on survival remained after correction for the age-adjusted International Prognostic Index (aaIPI).

Conclusions

Treatment of senior patients with aggressive NHL proved to be complex and full of risks. Not only could standard therapy be applied less often with a subsequent independent negative impact on overall survival, the high toxicity rate and the impossibility of the majority of patients to complete treatment, implies that better treatment strategies should be devised including a proper selection of senior patients for this aggressive chemotherapy.

Introduction

Haematopoietic and lymphoid tissue malignancies represent around 7% of all new malignancies and deaths of malignancies in Europe.[1] Aggressive B-cell non-Hodgkin lymphoma (NHL) is the most common haematopoietic and lymphoid tissue neoplasm in adults in almost all populations worldwide, and occurs frequently in elderly patients.[2]

For patients with advanced stage aggressive B-cell NHL, aggressive chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) is the first choice of treatment.[3,4] In the most recent decade, however, the addition of rituximab completes the standard treatment.[5,6] Older patients receive chemotherapy less frequently. Moreover, dose intensity and the number of applied cycles has been described to be inferior as compared to younger patients.[7-10] This may be caused by serious co-morbidity, poor performance status and lower resilience.[9]

Since elderly are often not or only selectively included in clinical trials,[11-14] evidence-based guidelines are mainly based on results of treatment in middle-aged, relatively 'fit' patients. Management of cancer in elderly may need to be adapted in case of aggressive local or adjuvant and systemic treatment. In-depth studies with data from population-based cancer registries as a sampling frame should give insight into determinants of treatment and survival.

The aim of this study was to investigate treatment, treatment tolerance, motives for suboptimal treatment and outcome in elderly patients, aged over 75 years, with advanced stage aggressive non-Hodgkin lymphoma (NHL).

Patients and methods

Study population and data collection

Population-based data from 5 regional Dutch cancer registries was used; these registries cover almost 8 million people and record data on patients newly diagnosed with cancer in all hospitals in their region. Trained registrars routinely collect data on patient and tumour characteristics, histology, and Ann Arbor stage directly from the medical records. Furthermore, primary treatment (first six months) was registered as dichotomous variables (yes/no) for chemotherapy (CT) and radiotherapy (RT).

Additional data on co-morbidity (Adult Co-morbidity Evaluation 27 (ACE27) classification),[15] WHO performance status (Eastern Cooperative Oncology Group (ECOG)), living alone, living independently, motives for no therapy, chemotherapeutical regimens, adaptations of treatment and underlying motives, response,[16] and grade 3 or 4 toxicity (Common Toxicity Criteria, CTC)[17] was gathered from the medical records by trained data managers. The ACE-27 index is a validated 27-item co-morbidity index for patients with cancer. Information on 27 co-morbid conditions was gathered from the medical records, and classified as absent, grade 1 (mild decompensation), grade 2 (moderate decompensation) and grade 3 (severe decompensation). In case of two or more co-morbid conditions the highest grade was counted, and two or more grade 2 conditions were counted as grade 3. 'Living independently' also included patients who received home care. Patients living in institutions were classified as living dependently.

All patients aged 75 or older and diagnosed with advanced stage aggressive B-cell NHL and recorded in the five regional population-based cancer registries between 1997 and 2004 were included (N=515). Aggressive NHL was classified according the WHO classification,[18] and included all patients with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL) grade 3, and Burkitt lymphoma (BL). These neoplasms are documented from the medical records and registered in the cancer registry with ICD-O-3 morphology codes since 2001 (9698, 9673, 9684, 9679, 9678, 9687, 9826, 9675, and 9680) and ICD-O-2 morphology codes between 1989 and 2000 (9697, 9677, 9712, 9593, 9681, 9682, and 9672); For code 9672, tumours with localization in the stomach, bowel, lung, salivary glands, eye and skin were excluded.

Follow-up was completed until January 1st, 2009. In addition to passive follow-up via the hospital records, date of death or last contact was also obtained from the Municipal Personal Records Database (GBA). This institution collects data on vital status of all Dutch citizens. Survival time was defined as the time from diagnosis to death or end of the study. Patients who were alive at the end of the study were censored at January 1st, 2009.

Statistical analysis

Treatment of patients with advanced stage aggressive B-cell NHL aged 75 or older was described. Patient characteristics were documented by subgroup of therapy: at least six cycles of CHOP-like chemotherapy, less than six cycles of CHOP-like chemotherapy, other (=suboptimal) chemotherapy, no chemotherapy. CHOP-like chemotherapy was coded as CHOP, CHOP + rituximab, cyclophosphamide + hydroxorubicin + Vm-26 + prednisone + bleomycin + vincristine, and CHOP+methothrexate. Motives for suboptimal treatment and treatment adaptations were described. Furthermore, toxicity and response to treatment was reported per subgroup of therapy and age group.

Logistic regression was used to determine the independent effect of patient and tumour characteristics on the chance of receiving CHOP-like chemotherapy, and the chance of developing toxicities and treatment adaptations from CHOP-like chemotherapy. Crude survival rates were computed. The independent effects of patient characteristics and treatment on survival was analyzed with Kaplan-Meier curves and Cox regression analysis. Multivariable survival analyses were performed to estimate the hazard ratio of death.

Statistical analyses were performed using SAS software (version 9.2, SAS Institute Inc., Cary, North Carolina, USA, 1999).

Results

Of all 515 elderly advanced stage aggressive NHL patients, 31 were excluded due to the fact that no additional data could be gathered because of missing or incomplete files. Furthermore, we excluded four patients who were diagnosed at autopsy and five patients who turned out to have an indolent NHL. The remaining 475 patients included in this study had a mean age of 81 years. Most of them (387) were diagnosed with diffuse large B-cell lymphoma (DLBCL), 64 with mantle cell lymphoma (MCL), 19 with grade 3 follicular lymphoma and 5 with Burkitt lymphoma.

Table 1. Patient characteristics per subgroup of chemotherapy

		Total	≥6 x CHOP-like CT	<6 x CHOP-like CT	Other CT	No CT	P-value
		N	%	%	%	%	
Number of patients		475	27	18	20	35	-
Sex	Males	235	32	20	15	32	0.004
	Females	240	21	17	25	37	
Age group	75-79	235	37	21	17	24	
	80-84	160	21	17	23	39	<0.0001
	85+	80	5	13	25	58	
Ann Arbor Stage	II	165	32	19	15	33	
	III	121	22	20	26	31	0.2
	IV	189	24	16	21	38	
NHL entity	DLBCL	387	26	20	17	36	
	MCL	64	25	8	41	27	-
	FL grade 3	19	37	16	21	26	
	Burkitt L	5	40	20	0	40	
ACE-27	0	128	34	14	14	38	
	1	143	27	19	25	29	
	2	126	23	24	22	31	0.04
	3	72	21	14	21	44	
	unknown	6	0	33	0	67	
CVD	yes	179	20	21	21	38	0.06
	no	290	31	16	21	32	
COPD	yes	69	26	10	25	39	0.3
	no	400	27	20	20	34	
Hypertension	yes	105	21	22	28	30	0.08
	no	364	29	17	19	36	
Diabetes	yes	57	23	12	19	46	0.3
	no	412	27	19	21	33	
CVA	yes	48	13	19	33	35	0.04
	no	421	29	18	19	34	
Previous malignancies	Yes	62	26	21	26	27	0.5
	no	407	27	18	20	35	
ECOG	0-1	193	39	21	18	22	
	2-4	121	12	12	25	52	<0.0001

	unknown	161	23	20	20	37	
Living independent	yes	304	31	18	21	30	
	no	41	10	17	17	56	0.01
	unknown	130	22	19	19	39	
Living alone	yes	152	24	16	30	30	
	no	187	32	18	18	33	0.006
	unknown	136	22	21	14	43	
Hb	normal	219	32	20	21	27	
	elevated	234	22	18	21	40	0.01
	unknown	22	23	9	9	59	
LDH ULN	≤1.00	142	31	23	20	22	
	>1.00	266	26	15	22	37	0.1
	unknown	67	19	21	16	43	

Legend: CT = chemotherapy, CVD = cardiovascular disease, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, ECOG = performance status, Hb = haemoglobin level, LDH = lactate dehydrogenase level, ULN = upper limit of normal

Treatment of elderly NHL patients, and characteristics associated with standard therapy

Only 126 (27%) of the elderly patients received the standard therapy of at least 6 cycles of CHOP-like chemotherapy. Eighty-seven (18%) patients received less than 6 cycles CHOP-like chemotherapy, 20% received other (suboptimal) chemotherapy, and 35% received no chemotherapy. The percentage of patients receiving at least 6 cycles of CHOP-like therapy decreased from 37% of those aged 75-79 to only 6% of patients aged 85+ (figure 1). Patient characteristics by subgroup of therapy are described in table 1. Female sex, high age, co-morbidity, poor performance status, living dependently, living alone, and low haemoglobin levels were all associated with suboptimal or no chemotherapy. After adjustment for other variables, age and performance status were independently associated with receiving CHOP-like chemotherapy. In the investigated period only 23 (11%) NHL patients received rituximab combined with their CHOP-like chemotherapy.

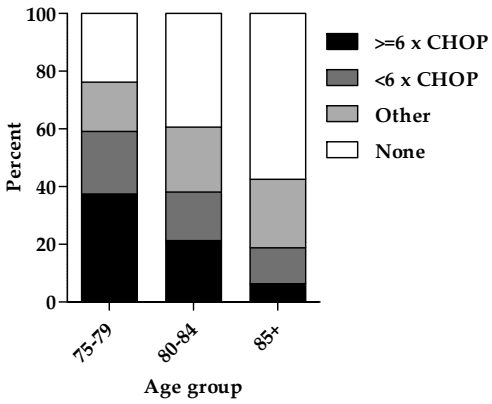

Figure 1. Chemotherapy by age group

Motives of suboptimal or no chemotherapy

Motives for suboptimal (other than CHOP-like) or no chemotherapy are listed in table 2. The most common reasons for withholding chemotherapy were refusal by patient/family (23%), poor performance status (19%) or estimated short life-expectancy (12%). For suboptimal chemotherapy these were high age (26%) or an unknown reason (32%).

Table 2. Motives for suboptimal chemotherapy

	No chemotherapy	No CHOP-like chemotherapy
Refused by patient or family	23%	4%
Poor performance status	19%	10%
Short life expectancy	12%	2%
High age	9%	27%
Other policy	9%	16%
Co-morbidity	8%	5%
Deceased before treatment was possible	7%	0%
Unknown	7%	32%
Other	6%	3%

Adaptations of therapy and their motives

76% of all patients receiving CHOP-like chemotherapy could not complete the scheduled standard treatment. For most patients this was an adaptation in the number of chemotherapy cycles (59% completed at least 6 cycles). Furthermore, 10%

had initial dose reductions and another 21% had dose reductions during treatment. Dose delays occurred in 23% of patients and the chemotherapeutical regimen was changed to a milder regimen in 10% of cases. In 53% of the cases the motive for adaptation was toxicity, mostly haematological toxicity (table 3). After adjustment for other variables (sex, co-morbidity, performance status, living independently, living alone, BMI, lactate dehydrogenase (LDH) and haemoglobin (Hb) level), age was the only factor associated with receiving less than six cycles of CHOP-like chemotherapy.

Table 3. Motives for treatment adaptations for patients receiving CHOP-like chemotherapy

Haematological toxicity	22%
Infectious toxicity	8%
Neurological toxicity	8%
Other toxicity	16%
Requested by patient or family	5%
Poor performance status	9%
Unknown	13%
Other	19%

Toxicity and response to treatment

Grade 3 or 4 toxicity occurred in 68% of patients receiving CHOP-like therapy, but also in 40% of patients receiving milder regimens. In more detail, 39% of patients receiving CHOP-like therapy experienced haematological toxicity, 11% cardiovascular toxicity, and 23% infections. Among patients receiving CHOP-like therapy the percentage experiencing toxicity increased with age, from 64% in age group 75-79 years, to 72% in patients aged 80-84, and 86% in patients aged 85 years and older. Toxicity also increased from 64% among those with high performance status to 86% among those with poor performance status. Complete remission was achieved in 64% of patients receiving at least 6 cycles of CHOP-like chemotherapy, and decreased towards 25% of those receiving less than six cycles. Complete remission rate was similar in all age groups. Of the patients with a complete remission after 6 or more cycles of CHOP-like therapy 43% had a recurrence of disease in our study period, with a mean time between diagnosis and recurrence of 22 months. Thirty percent of patients receiving less than six cycles of CHOP-like therapy had a recurrence of disease after complete remission (time between diagnosis and recurrence was 16 months). Suboptimal

chemotherapy resulted in a complete remission in 14% of the patients, of whom 71% had a recurrence of disease, with a mean time between diagnosis and recurrence of 25 months.

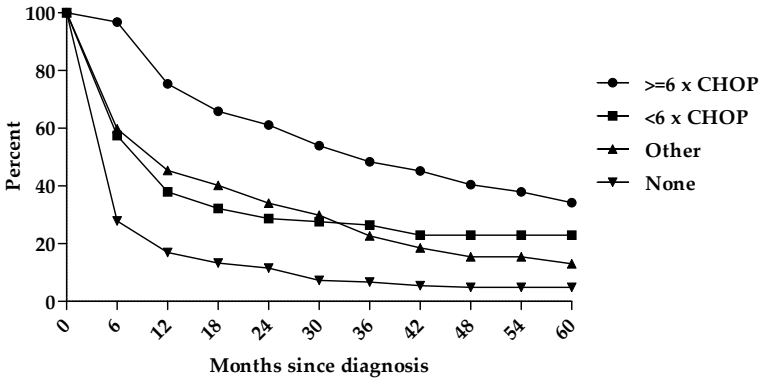

Figure 2. Overall survival of advanced stage aggressive NHL, by therapy group

Overall survival

Eighty-nine percent of all patients died during the study period. Five-year overall survival was 17% for the total group of NHL patients. Overall survival by subgroup of therapy is shown in figure 2. Six months after diagnosis, 97% of patients who received 6 or more cycles of CHOP were alive. This percentage decreased to 57% of patients who received less than 6 cycles, 60% of patients receiving other chemotherapy, and 28% of those not receiving chemotherapy. Five-year survival rates were 34%, 23%, 13% and 5%, respectively.

Survival was negatively influenced by high age, advanced stage, co-morbidity, poor performance status, low haemoglobin levels, high LDH levels, and suboptimal treatment. In multivariable analyses high stage, poor performance status, elevated LDH, and suboptimal therapy were independently associated with lower overall survival of elderly NHL patients (table 5). No statistical significant interaction between age and therapy was found. After correction for the age-adjusted International Prognostic Index (aaIPI)[19] the effect of therapy (in 4 subgroups) was independently associated with survival (HR = 1.7, 1.5, and 4.2 for <6 cycles CHOP-like, other chemotherapy and no chemotherapy, respectively compared to ≥6 cycles CHOP-like chemotherapy).

Table 5. Univariate and multivariable overall survival

		Univariate		Multivariable	
		HR	95%CI	HR	95%CI
Age group	75-79	1	-	1	-
	80-84	1.3	1.0-1.6	1.1	0.8-1.4
	85+	1.7	1.3-2.2	1.4	1.0-2.1
Ann Arbor Stage	II	1	-	1	-
	III	1.3	1.0-1.7	1.4	1.0-2.0
	IV	1.5	1.2-1.9	1.6	1.2-2.2
ACE-27	0	1	-	1	-
	1	1.1	0.8-1.4	1.3	0.9-1.8
	2	1.0	0.8-1.3	1.1	0.8-1.6
	3	1.5	1.1-2.0	1.4	0.9-2.1
ECOG	0-1	1	-	1	-
	2-4	2.2	1.7-2.8	1.5	1.1-2.0
Hb	normal	1	-	1	-
	elevated	1.4	1.2-1.7	1.1	0.8-1.4
LDH ULN	≤1.00	1	-	1	-
	>1.00	1.8	1.4-2.2	1.9	1.5-2.6
Therapy	≥6 x CHOP-like CT	1	-	1	-
	<6 x CHOP-like CT	1.7	1.3-2.3	1.8	1.2-2.8
	Other CT	1.8	1.3-2.4	1.4	0.9-2.1
	No CT	3.8	3.0-4.9	4.4	3.0-6.4

Legend: ECOG = performance status, Hb = haemoglobin level, LDH = lactate dehydrogenase level, ULN = upper limit of normal

Discussion

In daily practice the application of standard therapy (CHOP-like chemotherapy) could be achieved in a minority of only 45% of patients aged 75 or older. Not receiving chemotherapy was often due to refusal by patient/family, poor performance status or estimated short life-expectancy. Of all patients receiving CHOP-like chemotherapy only 59% could complete at least 6 cycles. The majority of patients receiving CHOP-like therapy suffered from severe toxicity (68% with grade 3 or 4), but this was also frequent (40%) in patients receiving milder regimens. Complete remission was achieved in 64% of patients receiving at least 6 cycles of CHOP-like chemotherapy, but 43% of these had a recurrence. The independent effect of therapy on survival remained after correction for the age-adjusted International Prognostic Index (aaIPI).

While cancer diagnosis is likely to decrease life expectancy in the majority of younger patients, the same consideration may not always be true for older people. Life expectancy in elderly cancer patients is a function of age, disability and co-morbidity, along with the cancer type and stage. Therapeutic decision-making involves a delicate balance among all these factors, evaluation of treatment-related complications and the overall effects of cancer and cancer treatment on expected survival and quality of life.[8,10,15,20-23] Therefore, treatment choice should be tailored to the individual patient. Our study confirms that in elderly patients, age, stage, co-morbidity, performance status, living independently, living alone and Hb levels all negatively influenced the choice for optimal cancer treatment with subsequent negative impact on survival. Furthermore, patient's refusal is also a prominent factor in treatment decisions (23%).

Earlier studies have shown that only 60% to 80% of patients aged 60 years or older, with aggressive NHL, received chemotherapy. [7,8,10] Our study confirms this underuse of chemotherapy in those patients. Maartense et al. showed that anthracycline-based chemotherapy was applied less frequently in elderly (≥70) patients (26%),[8] and Thieblemont et al. showed that only 4% of the patients aged 80 years and older received CHOP/RCHOP.[24] The higher percentage (45% for age 75+ and 32% for age 80+) in our study is probably due to the fact that we studied only patients with aggressive B-cell lymphoma and a later period of study. In our study monoclonal antibodies (rituximab) were only used in a rather small proportion of patients (5%). Therefore, we could not document the effect of this promising new therapy[25] in the older population. Further studies should investigate whether this small proportion of patients receiving rituximab is due to late introduction of this therapy, or whether older patients are denied a possible successful therapy.

In our study, adaptations of treatment were often related to (haematological) toxicity, and were needed in 72% of patients who were selected for CHOP-like chemotherapy. Physiologic modifications of body function are known to occur with age and may interfere with cancer treatment, e.g. decreased bone marrow reserve, decreasing renal excretion, liver size, blood flow, albumin production, cytochrome P450 function, and accumulation of body fat. These changes have important impact on the pharmacokinetic processes, and can lead to potentially harmful consequences.[20-22] This is probably the cause of the high rate (68%) of grade 3 and 4 toxicity in our

elderly population. However, despite the increased susceptibility of the elderly, dose of anticancer drugs is rarely adapted before chemotherapy is started.[22] In our study, 10% of the elderly had a dose reduction before start of chemotherapy. It is important to maintain dose intensity because of the steep dose-response curve,[8] some toxicity is acceptable but it should be managed very carefully. Older patients appear to be at higher risk for cardiotoxicity, haematological toxicity and infections.[22] Some threats may be prevented or reduced by proper supportive care, e.g. growth factors and prophylactic antibiotics. Others like cardiotoxicity, mucositis and neuropathy ask for special attention at each visit.[21,22] Toxicities can influence quality of life, which is an important and relevant factor in elderly patients. However, an earlier trial has shown that CHOP chemotherapy did not further deteriorate quality of life, and that quality of life improved at the end of treatment.[26] In our study age turned out to be associated with not being able to tolerate at least 6 cycles of CHOP-like chemotherapy. However, due to the retrospective nature of our study we could not evaluate all factors that might be predictive for chemotherapy tolerance. This indicates that the selection of patients for toxic chemotherapy like CHOP needs to be improved. Comprehensive geriatric assessment (CGA) may be helpful for identifying which patients are at high risk for severe toxicities.[22,27] A major problem of CGA is that this is a time consuming procedure and requires the availability of trained (geriatric) personnel. Recently, some attempts have been made to make shorter versions of CGA test, e.g. to make a pre-selection of possible frail patients.[28,29] Furthermore, CGA should be validated for this specific patient group.

In our study 64% of the (75+) patients receiving at least six cycles of CHOP-like therapy achieved complete remission. This is in line with a Dutch study from the eighties reporting a CR rate of 57% (age 70+) who received chemotherapy including anthracyclin,[8] and with Israel reporting a CR rate of 59% (80 or older).[23]

Our 5-year survival rates (17%) were in the lower end of the range of earlier (population-based and single institution) studies (18-38%).[8,24] This is probably due to the higher age limit and selection of only aggressive NHL with advanced stage in our study. The following well described patient-related variables may have an independent prognostic impact in elderly NHL patients: co-morbidity, gender, stage, performance status, haemoglobin level, and serum LDH level.[7,10,19,30-33] These factors were also related with poorer survival in our population. In previous studies,

increasing age was also negatively associated with overall survival for patients with aggressive NHL.[7,8,15,32,34] This was also found in our univariate analyses, but after correction for stage, co-morbidity, performance status, Hb level, LDH level and treatment, the prognostic effect of age disappeared. The negative influence of increasing age on overall survival in other studies could therefore be due to factors which correlate with age and for which we corrected. Although treatment is strongly related with the above mentioned patient characteristics, the independent effect of therapy on survival remained after correction for the age-adjusted International Prognostic Index (aaIPI).

This study gives a rather unique insight into everyday practice, motives for treatment decisions, adaptations of treatment, toxicity, and treatment outcome in unselected elderly NHL patients. However, we should keep in mind that this is a retrospective observational study in which there was selection of the fittest elderly for treatment. However, even in patients who were selected to be fit enough for undergoing CHOP-like chemotherapy, 59% could not complete at least 6 cycles. Furthermore, not all characteristics could be retrieved from the medical records. Some variables like performance status were often missing. In addition, Repetto et al. suggested that ADL and IADL are more sensible than ECOG performance score alone and that many aspects of functional impairment are not fully recognized by ECOG performance score.[27] Another limitation was the fact that we did not gather information about the use of medications. Therefore, we could not study the drugs-drugs interactions. However, use of medication generally has a high correlation with co-morbidity. Unfortunately, we did not document whether patients received supplemental therapies. Supplemental therapies could have influenced dose-intensity and the development of toxicities, and therefore have interfered with our results.[35] Prospective studies are needed, not only for giving insight into the risks and benefits of treatment of this group of patients with a short life expectancy, but also for evaluating the predictive value of patient characteristics. This would enable physicians and elderly patients to balance benefits, efforts and harm on a more individualized basis.

In conclusion, treatment of senior patients with aggressive NHL proved to be complex and full of risks. Not only could standard therapy be applied less often with a subsequent independent negative impact on overall survival, the high toxicity rate

and the impossibility of the majority of patients to complete treatment, implies that better treatment strategies should be devised including a proper selection of senior patients for this aggressive chemotherapy.

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5.3

The influence of prevalent diabetes mellitus on treatment outcome in non-Hodgkin lymphoma

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Abstract

Background

With an increasing prevalence of diabetes mellitus and non-Hodgkin lymphoma (NHL), the number of patients suffering from both diseases is growing. Our aim was to investigate the influence of diabetes on the treatment and outcome of NHL.

Patients and methods

Information was collected from the medical records of all patients with both NHL and diabetes (N=97) and a random sample of NHL patients without diabetes (N=106) newly diagnosed and recorded in the population-based Eindhoven Cancer Registry (1997-2004).

Results

Diabetic NHL patients more often needed dose-adjustments (23 vs. 11%), delay between cycles (31 vs. 17%), and decrease in the number of cycles (40 vs. 23%) as compared to those without diabetes. This resulted in a lower dose-intensity of adriamycine and vincristine. Treatment-related toxicity was more frequent in diabetics (mainly hyperglycaemia), whereas haematological toxicity, cardiovascular diseases, infections and neurotoxicity did not differ. Although overall survival was dismal for diabetic patients with indolent NHL, this difference disappeared after adjustment for age.

Conclusions

Although in diabetic NHL patients the dose-intensity of chemotherapy was lower and treatment-related toxicity occurred more often, no independent influence of diabetes on overall survival was observed.

Introduction

Due to ageing of the population and the increasing prevalence of obesity, the incidence of diabetes mellitus is rising.[1,2] In recent decades a rising incidence of NHL was also observed.[3,4] Earlier studies have shown that diabetic NHL patients are treated less intensively and have a worse prognosis compared to those without diabetes.[5-10] Diabetes might negatively influence anti-cancer treatment as well as life expectancy itself. In addition, treatment with chemotherapy can enhance complications of diabetes, and further reduce survival. The influence of diabetes on dose, number of cycles and treatment complications in NHL patients has to our knowledge never been subject of any scientific research.

Before 2001 rituximab was not yet implemented in the treatment regimen of NHL.[11] Nowadays, indolent NHL is generally treated with rituximab, cyclophosphamide, vincristine and prednisone (R-CVP),[12,13] whereas chemotherapeutic treatment of aggressive NHL also contains adriamycine (R-CHOP)].[14-16] From these chemotherapeutic drugs, we would expect more adverse effects (cardiotoxicity, neurotoxicity and hyperglycaemic crises) among diabetic patients, due to the pathophysiology of diabetes.[17,18]

The aim of this study was to investigate the effect of diabetes on choice of treatment, dose, treatment-related toxicity and outcome of non-Hodgkin lymphoma in unselected patients.

Patients and methods

Study population and data collection

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.4 million inhabitants, 10 general hospitals and two radiotherapy institutes. Registration clerks actively collect data on diagnosis, topography, histology, stage and initial treatment from hospital medical records. The medical record is regarded as the most complete source of information on the patient's past and current health status.[19] Since 1993 the Eindhoven Cancer Registry also registers the presence of co-morbidity with prognostic impact. To record co-morbidity, a modified version of the widely used Charlson co-morbidity index is used.[20] Co-morbidity (e.g. diabetes) was defined as diseases that were present at the time of cancer diagnosis. Co-morbidities were registered as dichotomous

variables (yes/no), according to the medical history of the patient, use of relevant drugs and diagnostic work-up.

In the Netherlands, diabetes mellitus is being diagnosed according to guidelines of the American Diabetes Association as having a fasting glucose level equal or above 7.0 mmol/L or a random plasma glucose level above 11.1 mmol/L.[21] NHL entities were defined according to the WHO-classification, 4th edition,[22] and included all indolent and aggressive B-cell neoplasms. Of all NHL patients aged 50 or older and diagnosed between 1997 and 2004 in the southern part of the Netherlands (N=1963), 169 (8.6%) had diabetes. Of the patients with NHL and diabetes, 46 patients with chronic lymphatic leukaemia (CLL) without lymphatic localizations were excluded, as were 26 because the medical record could not be traced. In the random selection of controls (NHL without diabetes, N=170), 64 patients were excluded for the same reasons (29 CLL, 35 no record available). This resulted in 97 patients with both NHL and diabetes, and 106 NHL patients without diabetes. We used a random sample of non-diabetic NHL patients, instead of matching, because we wanted to determine the independent effect of diabetes and age after multivariable correction. Since elderly patients, especially those with diabetes, tend to have a high prevalence of cardiovascular disease (CVD) and hypertension, we adjusted our analyses for these diseases. CVD included myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft, peripheral arterial disease and cerebrovascular diseases.

Additional information was collected from medical records. This included performance status according to WHO-criteria,[23] biochemical and body parameters at diagnosis (haemoglobin (Hb) and lactate dehydrogenase (LDH) level), smoking, body mass index (BMI), prognostic indices for aggressive and indolent lymphoma, detailed information on treatment of NHL, adjustments in treatment, toxicity,[24] response to treatment, date and cause of death. BMI was classified as: low <18 kg/m^2, normal 18-25 kg/m^2, overweight 26-30 kg/m^2 and obese >30 kg/m^2. Hyperglycaemic toxicity was defined according to NCI common toxicity criteria as a serum glucose concentration between 13.9 and 27.4 (grade 3) and above 27.4 mmol/L (grade 4). Hypoglycaemic toxicity was defined as a serum glucose concentration between 2.2 mmol/L and 1.7 mmol/L (grade 3) and below 1.7 mmol/L (grade 4).[24] Stage of NHL was classified using the Ann Arbor staging system.[25] Response to treatment of

NHL was extracted from medical files, whereby the judgment of the physician was considered to be conclusive and assessed in accordance with the Cheson-response criteria.[26] For the prognostic indices, we used the International Prognostic Index (IPI) in case of aggressive NHL and the Follicular Lymphoma International Prognostic Index (FLIPI) for indolent NHL.[27,28]

In addition to data on follow- up of vital status in the hospital records, information on vital status was obtained actively from the Municipal personal records database (GBA). Survival time was defined as the time from diagnosis to death or the end of follow-up. Patients who were still alive were censored on the date of last follow-up.

Statistical analysis

First, NHL patients with and without diabetes were compared with respect to the proportion of patients receiving chemotherapy (CT), regimen and dose reduction, number of cycles, and time between courses. Furthermore, we analysed the response to this treatment and toxicity with the Chi-square test. A P-value < 0.05 was regarded as significant. The independent effect of diabetes on overall survival of NHL was estimated using proportional hazards analyses. The hazard rates for death (Model A, adjusted for age) were further adjusted for performance status (Model B) and also for stage, grade, Hb-level, LDH level (Model C) and prevalence of cardiovascular diseases (CVD, Model D). Hazard ratios with 95% confidence intervals are presented.

The SAS computer package (version 9.1) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1999).

Results

The characteristics of the diabetic and non-diabetic NHL patients are shown in table 1. Median age was significantly higher in the diabetes group (72 vs. 69 years). Furthermore, smoking was less common among diabetic patients. In diabetic patients a higher BMI, cardiovascular disease, hypertension and poor performance status, was found more frequently. For aggressive NHL patients IPI score was higher in diabetic patients. The majority of NHL consisted of diffuse large B-cell lymphoma.

Table 1. Characteristics of diabetic and non-diabetic NHL patients

	Diabetes	No diabetes	P-value
Number of patients	97	106	-
Median age (range)	72 (52-88)	69 (50-87)	0.0003
Sex	Males: 48%	Males: 57%	0.2
Stage of NHL	I: 33% II: 12% III: 20% IV: 30% Unknown: 5%	I: 35% II: 9% III: 20% IV: 33% Unknown: 3%	0.9
Grade of NHL	Indolent: 31% Aggressive: 69%	Indolent: 35% Aggressive: 65%	0.5
Grade combined with Stage	Indolent stage I/II: 14% Indolent stage II/IV: 15% Aggressive stage I: 24% Aggressive stage II/III/IV: 41% Unknown: 5%	Indolent stage I/II: 16% Indolent stage II/IV: 17% Aggressive stage I: 21% Aggressive stage II/III/IV: 43% Unknown: 3%	0.9
IPI for aggressive NHL	1: 7% 2: 12% 3: 19% 4: 12% Unknown: 49%	1: 25% 2: 14% 3: 6% 4: 13% Unknown: 42%	0.06
FLIPI for indolent NHL	1: 13% 2: 10% 3: 7% 4: 7% Unknown: 63%	1: 14% 2: 24% 3: 16% 4: 5% Unknown: 41%	0.4
Tobacco consumption	Current smoker: 15% Previous smoker: 24% Non-smoker: 35% Unknown: 27%	Current smoker: 33% Previous smoker: 9% Non-smoker: 44% Unknown: 13%	0.0002
BMI categorized	Low: 19% Normal range: 31% Overweight: 31% Obese: 22%	Low: 19% Normal range: 51% Overweight: 22% Obese: 9%	0.005
CVD	39%	23%	0.01
Hypertension	37%	23%	0.02
Mean Hb (mmol/L; range)	7.6 (3.9-10.7)	8.0 (3.1-10.4)	0.08
Mean LDH (U/L; range)	409.3 (32-3858)	408.5 (63-2450)	0.99
Performance status according to WHO-classification	0: 15% I: 29% II: 27% III: 18% IV: 0% Unknown: 11%	0: 31% I: 27% II: 17% III: 6% IV: 4% Unknown: 15%	0.002

Legend: NHL = non-Hodgkin lymphoma, IPI = international prognostic index, FLIPI = follicular lymphoma international prognostic index, BMI = body mass index, CVD = cardiovascular diseases, Hb = haemoglobin, g/dL, LDH = lactate dehydrogenate, U/L = upper limit of normal

Influence of diabetes on the treatment of NHL

NHL patients with and without diabetes received chemotherapy (CT) to a similar degree (68 vs. 69%) and the motives for not giving CT were similar, most frequently being an alternative treatment strategy (radiotherapy or a wait-and-see policy) and/or a low performance status. Almost 70% of the patients with CT (65% in the group with diabetes and 68% without diabetes) received the CHOP regimen. Other regimens used were rituximab-CHOP (R-CHOP, 2%, only in 2003 (11%) and 2004 (31%)), CVP (11%), cyclophosphamide, adriamycine, tenoposide, prednisone and bleomycine, vincristine (CAVmP/BV, 10%) and chloorambucil (2%).

Treatment adjustments of the CT administered were required in 71% of NHL-patients with diabetes versus in only 49% of patients without diabetes. These adjustments include mainly the number of cycles (40 vs. 23%; p=0.04), and to a lesser extent in dose (23 vs. 11%; p=0.09) and interval between cycles (31 vs. 17%; p=0.07). When stratifying according to stage and grade, the differences in treatment adjustments between diabetic and non-diabetic patients were less pronounced, but the numbers became small. Adjustment in chemotherapy occurred significantly more often in patients with aggressive NHL with than without diabetes (OR 3.5 (95%CI 1.5-8.1)). The reasons for treatment adjustments were similar for diabetic and non-diabetic patients (neurological toxicity being the most frequent reason (19%), data not shown). As a consequence, the cumulative doses of adriamycine and vincristine (mg/m^2) were significantly lower (197 mg/m^2 versus 281 mg/m2 and 6.0 mg/m^2 versus 9.0mg/m2, respectively) in patients with diabetes as compared to those without diabetes. The reduction in cumulative doses was most pronounced among patients aged 70 years or older (table 2). Radiotherapy was given equally to NHL patients with and without diabetes (31% and 29%, respectively). There were almost no adjustments of radiotherapy (3 out of a total of 61 patients receiving radiotherapy).

Table 2: Mean cumulative doses of adriamycine/vincristine for NHL-patients, according to age.

	Age	Number of patients	Diabetes		P-value
			Yes	No	
Adriamycine	<70	42	251[#]	287[#]	0.4
	≥70	39	163[#]	269[#]	0.005
Vincristine	<70	46	7.4[##]	8.5[##]	0.4
	≥70	45	5.2[##]	7.4[##]	0.04

Legend: [#] cumulative dose of adriamycine given (mg/m^2), [##] cumulative dose of vincristine given (mg/m^2)

Influence of diabetes on response to chemotherapy

Complete remission rate for patients receiving chemotherapy was rather low: 28% of NHL patients with diabetes and 31% of those without diabetes (p=n.s.), with no difference between aggressive and indolent NHL. Ten percent of patients who achieved complete remission suffered a relapse (no difference between diabetes and non-diabetes). Progression after partial remission or stable disease occurred more often among patients with diabetes (23%) compared to those without diabetes (20%, p=0.09), especially for patients with aggressive NHL.

Influence of diabetes on treatment-related toxicity

Eighty-seven percent of patients with diabetes suffered from grade 3 or 4 toxicity versus 66% for those without diabetes (p=0.007). The difference was mainly due to the frequent occurrence of hyperglycaemia in patients with diabetes. Few differences existed after chemotherapy in the two groups in haematological toxicity (50 vs. 50%), CVD (13 vs. 7%), infections (18 vs. 16%), neurological (23 vs. 21%) and urological problems (5 vs. 4%).

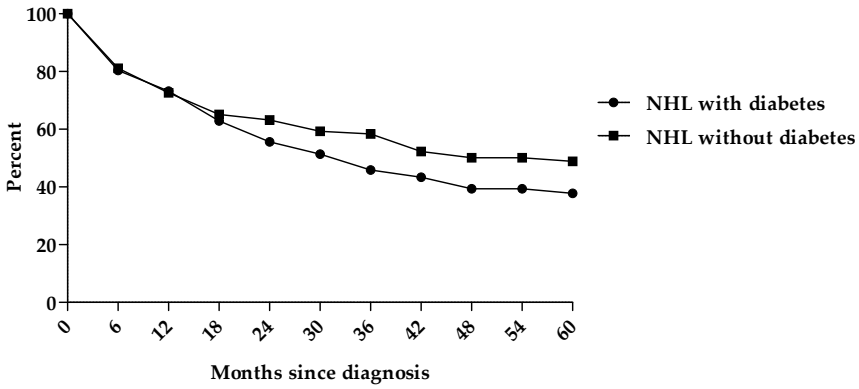

Figure 1. Overall survival of NHL patients, with and without diabetes mellitus

Influence of diabetes on survival of NHL patients

Overall survival of patients with NHL and diabetes was slightly poorer than that for patients without diabetes (p=0.04) (Figure 1), with 1- and 5-year overall survival of 73% and 44% for patients with diabetes and of 73% and 47% without diabetes. Diabetes mellitus was associated with a 1.4 times higher risk of mortality. However, after adjustment for age, the prognostic effect of diabetes disappeared. When stratified according to grade of NHL, only indolent lymphoma with diabetes was

associated with a lower survival compared to those without diabetes (table 3). After adjustment for age, the prognostic effect of diabetes also disappeared. Adjustment for other prognostic variables did not further influence the prognostic effect of diabetes. In aggressive NHL diabetes mellitus did not have a prognostic effect.

Table 3: Hazard ratio for diabetes on survival of NHL after adjustment for different prognostic factors

	Univariate	Model A	Model B	Model C	Model D
HR indolent NHL	2.0	1.7	1.2	0.6	0.5
CI 95%	1.1-3.9	0.9-3.3	0.5-2.9	0.2-1.8	0.1-1.6
HR aggressive NHL	1.2	0.9	0.9	0.7	0.8
CI 95%	0.8-1.8	0.6-1.1	0.5-1.5	0.4-1.3	0.4-1.3

Legend: HR = hazard ratio, CI 95% = 95% confidence interval, Model A = adjusted for age, Model B = adjusted for model A and socio-economic status, WHO performance status, Model C = adjusted for model B and stage, Hb, LDH, Model D = adjusted for model C and CVD

Discussion

In the present study the prevalence of diabetes among newly diagnosed unselected NHL patients was 8.6%, which is somewhat lower than exhibited in other studies.[6,8] The prevalence of diabetes in the same age-group in the general population is estimated at 11%.[28] The prevalence of diabetes in a Swedish population was 11%,[29] while being 18% in the United States.[30] The higher prevalence in the study from the US is likely due to the presence of more non-Hispanic blacks and Mexican-Americans who are ethnically more at risk for diabetes[30] and because this study covers a more recent period. Furthermore, although we assessed from medical records, which are more clinically precise than self-reported or administrative databases, we could have missed less severe diabetes. We found that in diabetic NHL patients, dose of chemotherapy was lower and treatment-related toxicity was more frequent resulting in a lower overall survival compared to NHL patients without diabetes. However, this dismal prognosis disappeared after adjustment for differences in age.

Diabetic NHL patients needed more adjustments in the number of cycles, drug dose and time-interval. Consequently, they were treated with a lower dose-intensity for adriamycine and vincristine. To our knowledge, this negative impact of diabetes mellitus on dose intensity has never been described before.

Treatment related-toxicity was significantly more prevalent in the diabetes group, mostly reflected by more hyperglycaemia due to the high dose steroid treatment. However, we did not find the expected higher frequency of neurological, cardiovascular and haematological toxicity in the diabetes group. This is in contrast with a recent report describing more frequent unexplained very toxic reactions among certain elderly NHL patients.[31] Our population-based study was carried out in a group of patients registered between 1997 and 2004 when CHOP was the first choice of treatment.[11] Meanwhile, changes have occurred by the introduction of rituximab. Our study seems nevertheless useful in evaluating the effect of diabetes on the treatment of NHL. In our study complete remission rate was rather low, which is probably related to the higher prevalence of low performance score and/or co-morbidity in this series of unselected patients and due to less effective treatment in the pre-rituximab era.

Co-morbidity in general has been described to be an important prognostic factor in the treatment of NHL,[6,7,10] although diabetes has only been documented in a few previous studies.[8,9] In these studies, NHL patients with diabetes had worse overall survival compared to those without diabetes, although no correction for tumour grade was performed in these studies. The poorer survival in diabetic patients might be due to several mechanisms: less aggressive treatment of cancer, higher complication rate of treatment, neglect of treatment of diabetes during treatment, an increased mortality risk due to the co-morbidity as such, and there could also be the presumptive role of insulin as tumour growth factor. Whether the less aggressive treatment, as reflected by the lower dose-intensity in elderly patients with diabetes, was justified or not remains a matter of debate and should preferably be tested prospectively. Furthermore, the effect on chemotherapy combined with rituximab should be investigated. In our study, overall survival was slightly worse for patients with indolent NHL and diabetes in univariate analysis. However, after adjustment for differences in age, the previously found prognostic effect of diabetes disappeared, after which adjustment for other prognostic variables did not further influence the prognostic effect of diabetes.

Our study of unselected patients, extracted data from a quality controlled cancer registry system and reflects everyday reality in the general health care environment of 6-12 years ago. Population-based data of co-morbidity in cancer patients are scarce and even with our approach we were stuck with a relatively small number

of patients. Larger, preferably prospective studies are needed to confirm our results.

In conclusion, NHL patients with diabetes received a lower dose-intensity of chemotherapy, and had more treatment related toxicity, but no independent influence of diabetes on overall survival was observed.

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Chapter 6

General discussion

Discussion

Our studies have visualised non-Hodgkin lymphoma patients in the daily clinical practice, as recorded in the population-based cancer registries in the Netherlands since 1989. The age-adjusted incidence has increased modestly for indolent mature B-cell and mature T- and NK-cell neoplasms, whereas it remained stable for aggressive mature B-cell neoplasms. Mortality was stable between 1989 and 2003, and has been decreasing since 2003. Relative survival has been rising slightly for patients with mature B-cell neoplasms, but remained stable for T- and NK-cell neoplasms. This has resulted in an increasing prevalence of NHL (17,597 in 2008). Survival for patients with NHL in Europe has improved during 1990-2004, but differences between geographical locations still exist. In a substudy in the south of the Netherlands the prevalence of autoimmune and chronic inflammatory disorders appeared to be higher among newly diagnosed patients with lymphoid malignancies during 1995-2007 than among other cancers. The follicular lymphoma international prognostic index (FLIPI) and Mantle cell lymphoma international prognostic index (MIPI) can stratify the prognosis of patients based on patient and tumour characteristics, we ascertained that these indices were also valid in unselected Dutch NHL patients. We found that adding or refining variables (such as co-morbidity) could improve the prediction of prognosis of these patients. Therapies in older patients deviated so much and so often from standard therapies that new policies should be developed for this growing group of elderly NHL patients. Treatment of elderly patients with aggressive NHL proved to be complex and full of risks, but not receiving standard therapy had a subsequent independent negative impact on overall survival. Thus the high toxicity rate and the impossibility of the majority of patients to complete treatment, implies that better aggressive treatment strategies should be devised including a proper selection of senior patients.

Long-term trends in incidence and mortality

In order to study the progress against cancer we investigated mortality and its determinants: incidence, treatment, and survival of NHL and of three major subgroups of NHL patients in the Netherlands. The incidence has been increasing for indolent mature B-cell and mature T- and NK-cell neoplasms (estimated annual percentage of change (EAPC) being 1.2% and 1.3%, respectively), but remained stable for aggressive mature B-cell neoplasms since 1989. We included all unspecified cases with the group of aggressive B-cell neoplasms, because it was most likely that these

unspecified cases belonged in this subgroup. Due to improvements in diagnostic tools, less unspecified cases were documented in recent time periods. Without the decrease in unspecified cases, the incidence of aggressive B-cell neoplasms would probably also have increased. Incidence rates in our study were comparable with those in Italy, the US and Scandinavia.[1,2] For several decades, there has been a marked increase in NHL incidence worldwide.[3-8] We elucidated that this rise in incidence in the Netherlands is particularly due to more indolent B-cell and T- and NK-cell neoplasms. The rise in incidence documented in Sweden, Denmark and the USA was especially marked between 1960 and 1990 (2%-4%); afterwards the incidence has been levelling off in some countries.[5] Our study showed a small rise in incidence between 1989 and 2007, but the levelling off was not visible (yet).

The increase in mortality until the early nineties and the later stabilization and decline was seen all over the world.[2,3,7] Since 2003 mortality is decreasing, probably due to smaller increases in incidence and improving survival rates in the subtypes with the highest prevalence. Prevalence of NHL was 11,143 in 2000[9] and increased to 17,597 at January 1st, 2008, or from around 46 to 86 per 100,000 inhabitants.

Aetiology

Little is known about the causes for the rise in incidence. Some of the classic risk factors for NHL have been identified such as immunodeficiency disorders, immunosuppression, infectious agents like hepatitis virus B, autoimmune disorders, and a positive family history of haematoid-lymphoproliferative malignancies.[5,10] Other risk factors such as exposure to chemicals, ultra violet exposure, dietary and lifestyle factors and blood transfusions might also be related to lymphoma development.[6] Co-morbidity is mostly studied as prognostic factor, but can also be used to study aetiological relations between specific co-morbidities and specific malignancies. Because the reported association between immunodeficiency disorders, immunesuppression, some infectious agents, and some autoimmune disorders on the one hand,[5,10,11] and haematological malignancies on the other hand, we investigated this association with data of the population-based Eindhoven Cancer Registry. We could confirm the positive association between several autoimmune and chronic inflammatory disorders (as derived from the medical record) and the various haematological malignancies, which suggests an etiological association between inflammatory diseases and malignancies in the immune system. Especially

the positive association between rheumatoid arthritis and most lymphomas (RR between 1.8 and 3.3), ulcers of stomach and duodenum and marginal zone lymphoma (RR 2.5 (1.5-4.2)), hepatitis and diffuse large B-cell lymphoma (RR 2.1), HIV and aggressive B-cell lymphoma (RR 16 (9.3-27)), and TBC and mantle cell lymphoma stood out (RR 2.6 (1.3-5.0)).

Long-term trends in relative survival

In the Netherlands, relative survival has been rising in all mature B-cell neoplasms; with 5 year relative survival rates for patients with indolent lymphoma rising from 67 to 75%, and for those with aggressive lymphoma from 43 to 52%. This thesis confirms previous findings of the improved survival of non-Hodgkin lymphoma in Italy and Ireland.[1,12] In addition, our study showed that survival kept improving in patients diagnosed during 2004-2007. The improved survival of patients with B-cell neoplasms in the latest period was probably caused by the increased use of more effective drugs such as the anti-CD20 monoclonal antibody rituximab. More accurate diagnostics and/or prognostic tools (e.g. International Prognostic Index (IPI)), aim to promote tailored treatment, and thus also better survival.[1,13-16] Better supportive care could also affect survival in patients with mature B-cell neoplasms,[17] through better endurance of therapy and also quality of life.[18] Then, improvements in the treatment of patients with a concomitant condition like HIV, even though its prevalence in the Netherlands was relatively low, may have contributed to improved survival since the end of the 90's.[19] Finally, there has been an overall pattern of more and better use of the treatment guidelines through the Dutch-Belgium Cooperative Group for Haemato-Oncology (HOVON, www.hovon.nl) the national organization of clinical trials for adults, and regionally within the now eight CCC's, possibly with some variation. The improvement in survival in the elderly patients with aggressive B-cell neoplasms was smaller, and started later, most likely related to the fact that younger patients tended to receive the new therapies sooner.[20] Patients with mature T- and NK-cell neoplasms showed a stable relative survival of 48%. The proportion of entities within the subgroup of T- and NK-cell has remarkably changed during the time periods and thus influenced survival. In 2009, consensus statements were formulated to improve diagnosis, staging, treatment and follow-up approaches for these patients.[21] Since 1985, HOVON has been conducting clinical trials to improve survival for all NHL patients, sometimes also including older patients. Nowadays, almost 25 studies are ongoing, which is likely to bring further progress.

We not only studied relative survival in the Netherlands, but used the EUNICE registry (a cooperation of eleven dedicated cancer registries across Europe, coordinated in Heidelberg at the German Cancer Research Center) to investigate survival for patients with NHL across Europe. Furthermore, data of the Surveillance Epidemiology and End Result (SEER) registry in the US was used to compare relative survival between European countries and the US.[22] In both Europe and the US, relative survival of NHL has been rising since 1990, but differences in survival were seen between the registries. In central European registries survival of patients aged younger than 45 improved substantially, resulting in similar relative survival in Central Europe, Western Europe and the US. Among patients of 45-54 years, we found similar relative survival in Western Europe and the US, but lower in Central European registries. For patients aged 55 and older relative survival in all European registries was lower than in the US for which several factors might be responsible: variation in the introduction of new therapies (like monoclonal antibody treatment (latest period) or stem cell transplantations), improvements of care of co-morbidity like HIV, through the use of prophylactic antibiotics, supportive care and adherence to guidelines. Furthermore, differences in health expenditures (e.g. much higher in Switzerland, France and the US) and in the level of access to specialized care could have affected detection and survival. Finally, differences between registries, for example related to coding of lymphoma entities could have led to another proportional distribution of lymphomas and there might also be variation in the availability of information about deaths.[22-24]

Our study could only document differences of survival and speculate about causal pathways. However, the effect of the difference in registry practices was probably much smaller than the therapeutic effects on survival differences observed in this study. Furthermore, the recently introduced monoclonal antibody therapies might only partly explain the higher relative survival in older American NHL patients,[22] because considerable differences in survival between the European registries and the US were already present in the era preceding introduction of monoclonal antibodies.

Validation of prognostic indices

The prognosis for patients with follicular lymphoma is heterogeneous and treatment options vary from "watchful waiting" to high-dose chemotherapy.[25] Patients with a poor prognosis should be considered for more aggressive and experimental therapies,

whilst on the contrary, those with a good prognosis may benefit from "watchful waiting" or less toxic regimens. Survival of patients with follicular lymphoma is influenced by several factors: firstly tumour-related factors like tumour diameter, number of nodal or extranodal sites, bone marrow involvement, stage, haemoglobin (Hb) level, lactate dehydrogenase (LDH) level and B-symptoms.[25-29] Furthermore, there are patient-related prognostic indicators like age and co-morbidity.[27,29-32] A prognostic index combines these factors and makes a selection for factors that can stratify patients based on their expected survival. The follicular lymphoma international prognostic index (FLIPI)[25] was designed with trial based data, that as usually only included younger and relatively fit patients. Prognostic models should be valid for daily clinical practice, allowing for stratification of patients and comparison of prognosis, and forming a basis for treatment decisions.[26] Validation in population-based settings is important because of the putative functionality of a prognostic index in daily practice. We therefore validated the predictive value of the FLIPI in a large dataset derived from the Eindhoven Cancer registry. FLIPI appeared to be reasonably valid, but could significantly be improved by a more refined coding of age and by including the presence of cardiovascular disease. The underestimation of age and co-morbidity in the original model can be explained by the fact that the proportion of elderly (with co-morbidity and a poorer performance status) is higher in general specialized practice.

The mantle cell international prognostic index (MIPI) is proposed to stratify survival of patients with mantle cell lymphoma.[33] This index was also based on patients included in clinical trials. For validation in a population-based setting we used the Eindhoven Cancer Registry. MIPI is a valid tool for risk stratification, comparison of prognosis, and treatment decisions in an unselected Dutch population-based setting, but could significantly be improved by a more refined coding of performance status and by including sex and the presence of B-symptoms as risk factors. External validation on an independent data set is warranted before broad application of this modified tool can be recommended. In several studies co-morbidity was found to be an independent prognostic factor for survival in NHL patients.[31,32] Although the presence of co-morbidity in general, and cardiovascular disease in particular, were significant prognostic factors in univariate analyses, these factors could not improve the prognostic performance of the MIPI. This is probably explained by the inclusion of performance status in the model, which is partly associated with the presence of

co-morbidity.[34] The higher proportion of patients with a poorer performance status in our population-based study could also be the reason for the relatively high impact of performance status in our model compared to the original model, because the original study contained only very few patients with a poor performance status.

Prognostic indices can stratify patients based on their prognosis. A disadvantage of these indices remains that they do not formulate reasons for poor prognosis. Therefore it remains debated whether the poor prognosis should be a reason for a more aggressive approach. When poor prognosis is associated with advanced age and presence of co-morbidity, patients are most likely at risk of being over-treated with a more aggressive approach.

Elderly

Non-Hodgkin lymphoma is highly prevalent in senior patients (mean age at diagnosis of 66 years). The population in the Netherlands is increasingly aging due to rising life expectancy and decreasing birth rates since the 1960s, resulting in an increased proportion of elderly people, and a higher number of (elderly) NHL patients. In the Netherlands Cancer Registry 2,676 patients aged 75 years and older, with aggressive mature B-cell neoplasms were registered during 1997 to 2004. Information on best treatment and prognosis is mostly gathered in clinical trials, showing that the best treatment for stage I aggressive B-cell neoplasms was a combination of radiotherapy preceded by three cycles of CHOP-like chemotherapy. Advanced stage patients should have received six to eight cycles of CHOP-like chemotherapy.[35,36] This treatment is not always feasible in everyday practice, where patients are older and suffer from concomitant conditions. In this thesis we used information of the Netherlands cancer registry for giving insight into treatment and outcome for unselected patients. We have shown that only 24% of the senior patients (75+ years) with stage I initially received chemotherapy and radiotherapy, compared with 46% of the patients aged 45-74 years. Furthermore, 65% of the senior patients (75+) with advanced stage NHL received chemotherapy, compared to 89% of the patients aged 45-74 years. Earlier population-based studies have also shown that only 60 to 80% of aggressive NHL patients aged 60 years or older, received chemotherapy.[31,37,38] In addition, we found that age and treatment both had an independent effect on survival. However, we have to keep in mind that selection of potentially fitter elderly for treatment has played a role.

In an in-depth study, we recorded detailed information on patient characteristics, specific treatment and its modifications and reasons for non-adherence to standard therapy from the medical records of 515 unselected patients with advanced stage aggressive B-cell neoplasms, diagnosed between 1997 and 2004. Only 27% received the standard therapy (at least six courses of CHOP-like chemotherapy) and 23 (11%) NHL patients received rituximab combined with their CHOP chemotherapy. Therefore, we could not document the effect of this new therapy in our population yet. In the group of patients aged 75 years and older, application of chemotherapy clearly decreased with the rise of age: 37% of the patients of 75-79 years received six or more cycles of CHOP-like chemotherapy, 21% at age 80-84 and only 5% in those aged 85+ years. Next to advanced age, serious co-morbidity, reduced performance status, female sex, living dependently or living alone, and low Hb levels were associated with suboptimal therapy. Reasons for not administering chemotherapy were mostly refusal of treatment by patient or family (23%), poor performance status (19%), or short life expectancy (12%). High age was the most common reason for suboptimal chemotherapy (26%), although chronological age is not supposed to be a unique criterium for acceptability of potentially curative aggressive treatments.[39,40]

Refusal of treatment by patients/family could be caused by fear of toxicity. In our population-based study serious toxicity was present in 68% of patients aged 75+ who received CHOP-like chemotherapy. Furthermore, adaptations of treatment, often related to (haematological) toxicity, were needed in 72% of patients who were selected for CHOP-like chemotherapy. Toxicities and the need for treatment adaptations of CHOP-like chemotherapy were not associated with the patient characteristics studied (age, sex, co-morbidity, performance status, living independently, living alone, Hb and lactate dehydrogenase (LDH) level). Comprehensive geriatric assessments could be helpful for indicating which patients are at high risk for toxicities, but they are not often applied explicitly.

Age, performance status, presence of co-morbidity, Hb levels, LDH levels, stage, and treatment were associated with overall survival, as was also shown in earlier studies.[31,34,37,41-44] Stage at diagnosis, LDH level, performance status and treatment were independent factors for overall survival, after correction of all other factors. The negative influence of increasing age on overall survival in other studies could be due to factors which correlate with age and for which we corrected. Although type

of treatment is strongly dependent on the above mentioned patient characteristics, an independent effect of therapy on survival remained after correction with age-adjusted International Prognostic Index (aaIPI). This all indicates that chemotherapy in elderly patients has two sides of a medallion: on the one hand high toxicity and frequent need for treatment-adaptations and on the other hand an independent improvement of survival for those who were able to complete the full treatment. Therefore, a good selection of elderly for aggressive chemotherapy is very important: avoiding undertreatment of fit elderly patients but also complications in frail patients.

Co-morbidity is known to be an important factor for treatment decisions and for prognosis in senior NHL patients. An earlier publication with data of the Eindhoven Cancer Registry has shown that serious co-morbidities were present in 61% of newly diagnosed patients with NHL aged 70 and older and in 43% of patients between 60 and 69 years, whereas 20% of patients of 16-59 years also suffered from one or more serious co-morbidities.[32] Furthermore, co-morbidity had a considerable influence on treatment and survival of NHL.[31,32,37] The most common serious co-morbidities were: cardiovascular diseases, other malignancies, and diabetes mellitus.[32] However, patients with serious co-morbidity are often excluded from clinical trials even when they include older patients. Population-based studies must therefore give insight into the treatment of patients with co-morbidity compared to those without co-morbidity and describe its influence on outcome. We therefore did a special study on the effect of diabetes mellitus on treatment and survival of NHL patients. Patients with diabetes and aggressive NHL had significantly more adaptations in therapy than patients with just aggressive NHL, which is in agreement with earlier reports studying general co-morbidity in elderly patients.[45] Treatment-related toxicity was significantly more prevalent in the diabetes group. In our study, this was mostly due to a higher prevalence of treatment-related hyperglycaemia, as was expected due to the high dose steroid treatment given, in the presence of diabetes. In univariate analysis overall survival was significantly worse for indolent NHL patients who also had diabetes. However, after adjustment for age, the previously found prognostic effect of diabetes disappeared. This finding contradicts earlier studies, in which diabetes was an independent prognostic factor in NHL patients.[45,46] Similar studies adjusted for the same variables, but we adjusted for age as a continuous variable instead of being dichotomized or for six age-groups.[46]

Conclusion

In conclusion, this thesis has shown that incidence has been rising for indolent mature B-cell and T- and NK-cell neoplasms. Relative survival was improving, but differences between geographical locations still exist, this could indicate that improved care may not be implemented in daily practice in every hospital yet. The rising incidence and survival has resulted in an increasing prevalence of NHL. These patients have a need for extra care, even after a long period following diagnosis. Therefore, extra attention for the organisation of this care is required. We could confirm the positive association between several autoimmune and chronic inflammatory disorders and the various lymphoid malignancies, which suggests an aetiological association between inflammatory diseases and malignancies in the immune system. Prognostic indices could give insight into the prognosis of a specific patient. In general practice special attention to age, co-morbidity and performance status is required in these indices. Treatment of elderly patients with aggressive NHL proved to be complex and full of risks. If therapies in older patients deviate so much from standard therapies, different policies should be developed for this growing group of elderly patients with aggressive NHL. In addition, not receiving standard therapy had a subsequent independent negative impact on overall survival, but the high toxicity rates and the impossibility of many patients to complete treatment, implies that less toxic treatment strategies should be devised including a proper selection of senior patients for this aggressive chemotherapy.

Future perspectives

Progress against the various cancers should be evaluated continuously, also in unselected, but well defined patients with NHL. Data of cancer registries can be used to study these factors on a regional, national and European base. Prospective studies of determinants and outcome of treatment, response, toxicity, recurrence, and survival of unselected patients who are either or not candidate for biological (generally expensive) therapy, is also required for adequate compensation by insurance companies. In the Netherlands this is already performed in the "Population-based HAematological Registry for Observational Studies" (PHAROS), an investigation of HOVON, three comprehensive cancer centres with their cancer registries and the Institute for Medical Technology Assessment (IMTA) to investigate the above mentioned aspects in non-Hodgkin lymphoma, multiple myeloma and

CLL and soon also CML. The prevalence of T- and NK-cell neoplasms is rather low and therefore it is difficult to study the effects and development of new therapies in these groups of patients. Furthermore, incidence and survival of T- and NK-cell neoplasms is not often described separately in the literature. As this thesis indicates, this subgroup of NHL is very different from the B-cell neoplasms; with a rising incidence and stable survival. International collaboration can be used to study these patients separately from B-cell neoplasms, for example to start within the EUROCARE study. Geographical differences in survival could indicate differences in health care and possibilities for improvement. Cancer registries can be used as a sampling frame for in-depth studies to evaluate whether adherence to treatment guidelines, use of multidisciplinary working groups, and size of hospitals can explain the survival differences.

There is little knowledge on causes of NHL, other than autoimmune and infectious diseases. Aetiological research is difficult due to the large lag time between cause and effect. Research in this area is more likely to be successful by separate entity of NHL, because the biological differences between these entities are large. For a sufficient sample size international collaboration is needed.

Prognostic indices can stratify (newly diagnosed) patients based on their expected prognosis before the treatment options are chosen. The question is when a poor prognosis cannot be any more an indication for a more aggressive approach, e.g. in case of advanced age and presence of co-morbidity. Besides determining factors that can predict the prognosis of patients, also factors that predict the response to treatment and toxicity should be included in treatment decisions. There is a great need to integrate these factors more systematically into everyday clinical practice.

Moreover, it is important to investigate which older patients can indeed tolerate intensive chemotherapy and who benefits from a palliative approach. Can prospective studies be designed for investigating the optimal treatment strategy for unfit elderly? To determine unfit or frail elderly the use of Comprehensive Geriatric Assessment (CGA) can be helpful, but this is a time consuming procedure and requires the availability of trained (geriatric) personnel. Recently, some attempts have been made to make shorter versions of a CGA test, e.g. to make a pre-selection of possible frail patients on the basis of easily available factors.[47,48] Comparative

studies in population-based settings should be able to identify which screening tool is best to select frail patients. Population-based research will thus remain important for research in senior and frail patients, supplementing data from clinical trials that even when they comprise elderly patients, are hampered by low inclusion rates of such patients. The regional Comprehensive Cancer Centres in the Netherlands can mediate between multidisciplinary working groups or organise meetings for specialists who would wish to enrol such patients with serious co-morbidities. Especially for elderly patients, but eventually for all patients it is as important to investigate the quality of life next to gain in survival time. Quality of life should be prospectively measured during and after treatment and also for long term (side) effects of treatment. In the Eindhoven Cancer Registry, a project called "Patient Reported Outcomes Following Initial treatment and Long term Survivorship" (PROFILES) has started to investigate the quality of life among patients with haematological malignancies prospectively.

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Summary

Introduction

Haematopoietic and lymphoid tissue malignancies represent around seven percent of all new malignancies and cancer deaths in Europe. In the Netherlands, 6,908 patients with haematopoietic and lymphoid neoplasms were diagnosed in 2007. Non-Hodgkin lymphoma (NHL) represents almost 50% of all haematopoietic and lymphoid tissue malignancies, and is subdivided into three major subgroups: indolent B-cell, aggressive B-cell, and T- and NK-cell neoplasms (1,706, 1,566 and 254 new patients in 2007, respectively).

Purpose of this thesis

The purpose of this thesis was to describe the progress against non-Hodgkin lymphoma in the Netherlands, since 1989. We therefore studied long term trends in incidence, treatment, mortality and relative survival in the Dutch cancer registries, and compared survival between several European cancer registries and the SEER database in the United States. Furthermore, we described the association between several autoimmune and chronic inflammatory disorders and the various lymphoid malignancies. Prognostic indices are important for stratification of patients according to their prognosis, and are a basis for treatment decisions. We validated two indices in unselected Dutch patients. In these studies we recognised the importance of age, co-morbidity and performance status for the prognosis of NHL patients. Therefore, we performed an in-depth study to evaluate treatment, response to treatment, toxicities and survival in elderly NHL patients.

Methods

We used data of cancer registries to visualise daily clinical practice in NHL patients. Most information on treatment and prognosis of NHL patients is gathered in clinical trials. This is a good method for evaluating treatment options in these selected patient groups, but might not be valid for everyday practice, where patients generally are older and frequently suffer from co-morbidity. Cancer registry data can give insight into treatment and outcome of these unselected patients.

Long-term trends in incidence and mortality

We evaluated whether incidence, treatment, mortality and survival has changed in the last twenty years (**chapter 2.1)**. We used the large population-based dataset of the Dutch National Cancer Registry. The number of patients with NHL increased from

2,321 in 1989 to 3,487 in 2007. Age-adjusted incidence increased significantly from 15.4 to 17.6 patients per 100,000 person-years. The trends in age-adjusted incidence differed per subgroup. Incidence has increased for indolent B-cell, from 8.7 per 100,000 in 1989 to 9.9 per 100,000 in 2007 for males and from 4.9 to 6.9 per 100,000 for females. The age-adjusted incidence rates for T- and NK-cell neoplasms were 1.4 and 0.7 in 1989, respectively for males and females, and increased to 1.7 and 1.0 in 2007. Incidence rates remained stable for aggressive B-cell neoplasms, at 9.3 for males and 6.1 for females. We included all unspecified cases in aggressive B-cell neoplasms, because this was the most probable subgroup. Excluding these patients would have led to biased results. Due to improvements in diagnostic tools the number of unspecified cases became smaller over time. The incidence of aggressive B-cell neoplasms would probably have increased when this unspecified group would have been excluded. Mortality of NHL remained stable at 6.2 per 100,000 between 1989 and 2003, and has been decreasing since 2003 to 4.8 per 100,000 in 2007.

Aetiology of NHL

Little is known about the causes for the rise in incidence. Some of the risk factors for NHL have been identified, such as immunodeficiency disorders, immunosuppression, infectious agents like hepatitis virus B, autoimmune disorders and a positive family history of haematoid-lymphoproliferative malignancies. Other risk factors such as exposure to chemicals, ultraviolet exposure, dietary and lifestyle factors and blood transfusions might also be related to lymphoma development. The relation between autoimmune and chronic inflammatory disorders on the one hand and haematological cancers on the other hand is covered in **chapter 3.1**. We could confirm the positive association between several autoimmune and chronic inflammatory disorders (as derived from the medical record) and the various lymphomas, which suggests an aetiological association.

Survival of NHL has improved

Relative survival has been rising for patients with B-cell neoplasms (five-year relative survival increased from 67% in 1989-1993 to 75% in 2004-2007 for indolent and from 43% to 52% for aggressive lymphoma), but remained stable (five-year relative survival was 48%) for T- and NK-cell neoplasms (**chapter 2.1**). The improved survival in the latest period for patients with B-cell neoplasms was probably caused by the increased use of more effective drugs, such as the anti-CD20 monoclonal

antibody rituximab. In the pre-rituximab period the improved survival is most likely due to several factors, such as the use of more accurate diagnostics and/or prognostic tools and better supportive care (haematological growth factors and prophylactic antibiotics).

The rising incidence and survival has resulted in an increasing prevalence of NHL, from around 7,000 in 1992 to 17,000 in 2007. As a result of this, the mean number of patients being under treatment or in follow-up per hospital has increased from 35 to 170.

In **chapter 2.2** differences in relative survival trends between countries within Europe and a comparison with trends in relative survival in the US was presented. Relative survival for patients with NHL in Europe has also improved during 1990-2004 (with a mean difference of nine percent units), but differences between geographical locations still exist. In central European registries, survival for patients younger than 45 years improved substantially, resulting in similar relative survival of these patients in Central Europe, Western Europe and the US in the last period (five-year relative survival of 74%, 79%, and 72%, respectively). Among patients of 45-54 years, we found similar relative survival in Western Europe and the US, but lower in Central European registries (five-year relative survival of 75%, 78%, and 56% in 2002-2004). For patients aged 55 and older, relative survival in all European registries was lower than in the US. Five-year relative survival of patients aged 55-64 was 49%, 65%, 73% in 2002-2004, respectively for Central Europe, Western Europe and the US. For age group 65-74, these percentages were 31%, 55%, and 67%, and for patients aged 75+ these were 23%, 39%, and 52%. Several factors might be responsible: variation in treatment (e.g. the introduction of monoclonal antibody treatment (especially in the latest period) or stem cell transplantations), and variation in improvements of care, of co-morbidity like HIV, the use of prophylactic antibiotics, supportive care, and adherence to guidelines. Furthermore, differences in health expenditures and in the level of access to specialized care could have affected detection and survival. Finally, differences between registries, for example related to coding of lymphoma entities could have led to another proportional distribution of lymphoma and there might also be variation in the availability of information about deaths. If any, the total effect of the difference between registries would have been much smaller than the survival differences seen in this study.

Relative survival of NHL improved in the Netherlands, as well as in other European countries and the US. Several study groups (like EORTC and HOVON) have studied new therapies and supportive care for NHL patients. This has resulted in an improved quality of care for NHL patients, although the differences between countries could indicate that this improved care may not be implemented in daily practice in every hospital yet.

Validation of prognostic indices

The prognosis of NHL differs greatly between patients. Prognostic indices, like the follicular lymphoma international prognostic index (FLIPI) and mantle cell lymphoma international prognostic index (MIPI), can stratify the expected prognosis of patients based on patient and tumour characteristics. Prognostic models should be valid for daily clinical practice allowing stratification of patients and thus forming a basis for treatment decisions. Validation in population-based settings is important because of the putative functionality of a prognostic index in daily practice. FLIPI and MIPI were developed with trial-based data that, as usually, only included younger and relatively fit patients.

We found that FLIPI was reasonably valid in a population-based cohort of patients. However, the index could significantly be improved by a more refined coding of age (3 instead of 2 subgroups) and by including the presence of cardiovascular disease (**chapter 4.1**). MIPI was also valid in unselected mantle cell lymphoma patients. Likewise, MIPI could significantly be improved by a more refined coding of performance status (5 instead of 2 subgroups) and by including the presence of B-symptoms and sex as risk factors (**chapter 4.2)**. In both validation studies the underestimation of age, co-morbidity and performance status can be explained by the fact that the proportion of elderly (with high age, co-morbidity and a poorer performance status) is higher in the general practice as compared to patient groups included in trials. External validation on an independent data set is warranted before broad application of these modified tools can be recommended. A disadvantage of these indices remains that they do not formulate reasons for poor prognosis. Therefore, it remains debated whether the poor prognosis should be a reason for a more aggressive approach.

Management of elderly patients

Non-Hodgkin lymphoma is highly prevalent in elderly patients (57% was 65 years or older at diagnosis). The population in the Netherlands is aging due to rising life expectancy and decreasing birth rates since the 1960s, resulting in a yearly increase in the number of elderly NHL patients. Of importance is that advanced age is known to be an important predictor of survival, and not all elderly patients receive standard therapies. Therefore, we studied these elderly patients in further detail. Clinical trials in the Netherlands and elsewhere have shown that the best treatment for stage I aggressive B-cell neoplasms was a combination of radiotherapy preceded by three cycles of CHOP-like chemotherapy, whereas for advanced stage six to eight cycles of CHOP-like chemotherapy is the treatment of choice. This therapy is not always tolerable for elderly patients and those with severe co-morbidity. Indeed, we have shown that only 24% of the elderly patients (75+ years) with stage I have received chemotherapy and radiotherapy as primary treatment, compared with 46% of the patients aged 45-74 years (**chapter 5.1)**. Furthermore, 65% of those with advanced stage NHL received chemotherapy as primary treatment, compared with 89% of patients aged 45-74 years. In addition, age and treatment both had an independent effect on survival. However, we have to keep in mind that selection of potentially fitter elderly for treatment has played a role in this retrospective population-based study.

An in-depth study concerning treatment and treatment outcome of these elderly patients is displayed in **chapter 5.2**. We recorded detailed information on patient characteristics, specific treatment and its modifications and motives for non-adherence to standard therapy from the medical records of 515 unselected patients with advanced stage aggressive B-cell neoplasms. Only 27% received the standard therapy (at least six courses of CHOP-like chemotherapy). Serious co-morbidity, reduced performance status, female sex, not living independently, living alone, and high haemoglobin (Hb) levels were all associated with suboptimal or no chemotherapy. The most common motives for not administering chemotherapy were refusal of treatment by patient or family (23%), poor performance status (19%), or short life expectancy (12%). High age was the most common reason for suboptimal chemotherapy (26%). In our population-based study grade three or four toxicity was present in 68% of patients aged 75+ who received CHOP-like chemotherapy and only 59% of patients who were selected for CHOP-like chemotherapy could complete the full treatment. Toxicities and the need for treatment adaptations of

CHOP-like chemotherapy were not associated with the patient characteristics studied (age, sex, co-morbidity, performance status, living independently, living alone, Hb and lactate dehydrogenase (LDH) level). Comprehensive geriatric assessments could be helpful for indicating which patients are at high risk for toxicities. Stage at diagnosis, performance status, LDH level and treatment were independent factors for overall survival, after correction for all other factors. Age did not influence survival independently and should therefore not be used as a single factor for treatment decisions. Furthermore, therapy had an independent effect on survival after correction for the age-adjusted International Prognostic Index. This all indicates that chemotherapy in elderly patients has two sides of a medallion: on the one hand high toxicity and frequent need for treatment-adaptations and on the other hand an independent improvement of survival for those who are able to complete the full treatment. Therefore, a proper selection of elderly for aggressive chemotherapy as CHOP is very important.

Co-morbidity appeared to be an important therapy-related factor in earlier studies of this thesis. In an in-depth study we showed that NHL patients with diabetes had significantly more adaptations in therapy than patients with aggressive NHL without diabetes (**chapter 5.3**). Although the dose-intensity of chemotherapy was lower in patients with diabetes, survival did not appear to be independently affected by diabetes. Treatment-related hyperglycaemia was significantly more prevalent in the diabetes group, as was expected due to the high dose steroid treatment given in the presence of diabetes.

Conclusion

In **chapter 6** the main results and perspectives for research and clinical management are discussed. The rising incidence and survival has resulted in an increasing prevalence of NHL. These patients have a need for extra care, even after a long period following diagnosis. Relative survival of NHL improved in the Netherlands, as well as in other European countries and the US. However, regional differences in survival still exist, especially in elderly patients. This could indicate that this improved care may not be implemented in daily practice in every hospital yet. Treatment of elderly patients with aggressive NHL proved to be complex and full of risks. Not receiving standard therapy has a subsequent independent negative impact on overall survival, but high toxicity rate and the impossibility of the majority of patients to complete treatment, implies that better treatment strategies should be devised including a proper selection of senior patients for this aggressive chemotherapy.

Samenvatting

Inleiding

Zeven procent van alle nieuwe tumoren en sterfte als gevolg van kanker in Europa wordt veroorzaakt door bloed- of lymfeklierkanker. In Nederland zijn in 2007 6.908 nieuwe patiënten gediagnosticeerd met dit type kanker. Lymfeklierkanker is een kanker die ontstaat, doordat cellen van het immuunsysteem (lymfocyten) ongeremd gaan delen. Lymfekliertumoren worden onderverdeeld in twee types, namelijk het Hodgkin lymfoom en het non-Hodgkin lymfoom (NHL). We bespreken in dit proefschrift alleen het NHL. Dit type wordt verder onderverdeeld in drie groepen. De eerste groep bestaat uit tumoren die ontstaan zijn uit een B-cel lymfocyt met een indolent karakter (langzaam groeiend). De tweede groep ontstaat ook uit B-cel lymfocyten, maar deze ziektes uitwikkelen zich agressief. De laatste (kleine) groep bestaat uit tumoren die ontstaan uit T- en NK-cel lymfocyten.

Doel van het onderzoek

Het doel van dit proefschrift is het beschrijven van de vooruitgang die de afgelopen twintig jaar is geboekt met betrekking tot preventie, diagnose en behandeling van NHL. Daarbij is specifiek gekeken naar het aantal nieuwe patiënten met NHL, de behandeling, de overleving en het aantal mensen dat aan deze ziekte is overleden. Verder zijn de overlevingskansen van patiënten met lymfeklierkanker in Nederland vergeleken met die in andere landen. Ook is de associatie tussen enerzijds auto-immuun- en infectieziekten en anderzijds lymfeklierkanker onderzocht. Omdat de overleving tussen patiënten onderling sterk kan verschillen, hebben we gekeken of met een index de overlevingskans van deze patiënten kan worden voorspeld. Tot slot hebben we de behandeling en overleving beschreven van patiënten van 75 jaar en ouder (een sterk groeiende groep in Nederland). De resultaten uit dit proefschrift kunnen gebruikt worden om de zorg voor NHL patiënten verder te optimaliseren.

Methode van onderzoek

Tijdens deze studie zijn patiënten bestudeerd bij wie tussen 1989 en 2007 de diagnose NHL werd gesteld. Hiervoor hebben we gebruik gemaakt van gegevens van kankerregistraties. Dit zijn databanken waarin gegevens zijn opgeslagen van alle patiënten met kanker, zodat een goed beeld is verkregen van de alledaagse klinische praktijk. Dit is vooral van belang, omdat informatie over het effect van een behandeling voornamelijk afkomstig is van specifieke klinische onderzoeken (trials). Deze onderzoeken bevatten meestal vooral jongere patiënten en patiënten

die geen bijkomende ziektes hebben. In de dagelijkse praktijk hebben we echter vaak te maken met oudere patiënten die naast NHL ook andere chronische ziektes hebben.

Veranderingen in de afgelopen twintig jaar in Nederland

In **hoofdstuk 2.1** worden de veranderingen beschreven in het aantal nieuwe patiënten met NHL, de behandeling, het aantal sterfgevallen en de overleving in de afgelopen 20 jaar. In Nederland steeg het aantal nieuwe patiënten met NHL van 2.321 in 1989 naar 3.487 in 2007. De voor leeftijd gecorrigeerde incidentie steeg van 15,4 naar 17,6 patiënten per 100.000 inwoners per jaar. Dit betekent dat iedere huisarts op dit moment wordt geconfronteerd met gemiddeld twee nieuwe patiënten in zes jaar vergeleken met 1,5 nieuwe patiënt twintig jaar geleden. De trend in het aantal nieuwe patiënten verschilt per subgroep. Voor indolente B-cel lymfomen steeg de incidentie van 8,7 naar 9,9 per 100.000 voor mannen en van 4,9 naar 6,9 per 100.000 voor vrouwen. Voor agressieve B-cel lymfomen bleef de incidentie stabiel (9,3 voor mannen en 6,1 per 100.000 voor vrouwen). Niet-gespecificeerde lymfomen hebben we ingedeeld in de groep van agressieve B-cel lymfomen, omdat dit de meest waarschijnlijke groep is waartoe deze tumoren zouden behoren. Door een verbeterde diagnostiek is het aantal niet-gespecificeerde lymfomen gedaald. Mogelijk kan dit de stabiele incidentie van de agressieve B-cel lymfomen verklaren. De incidentie van T- en NK-cel lymfomen steeg sterk van 1,4 en 0,7 in 1989 naar 1,7 en 1,0 per 100.000 in 2007, respectievelijk voor mannen en vrouwen. Ondanks de stijging in incidentie bleef het aantal sterfgevallen ten gevolge van NHL stabiel tussen 1989 en 2003 (6,2 per 100.000). Na 2003 is dit aantal gedaald naar 4.8 per 100.000 in 2007.

Oorzaken van NHL

Kennis over risicofactoren voor NHL en de gestegen incidentie is beperkt. Mogelijk spelen infecties, auto-immuunziekten, een verzwakt of onderdrukt immuunsysteem en erfelijke factoren een rol. In **hoofdstuk 3.1** hebben we onderzocht of er een associatie bestaat tussen enerzijds verschillende auto-immuun- en chronische ontstekingsziekten en anderzijds verschillende kankertypes. Het percentage patiënten, dat al een auto-immuun- of chronische ontstekingziekte had ten tijde van de diagnose 'kanker' was hoger bij lymfeklierkanker dan bij andere kankertypes. Dit impliceert dat er mogelijk een oorzakelijk verband is of dat een gemeenschappelijke oorzakelijke factor een rol speelt.

Overleving is verbeterd

Relatieve overleving is een benadering voor de ziektespecifieke overleving. Ziektespecifieke overleving zegt iets over de kans om aan NHL te overlijden, doordat er gecorrigeerd is voor andere doodsoorzaken. In **hoofdstuk 2.1** hebben we gezien dat de relatieve overleving van B-cel tumoren tussen 1989 en 2007 is gestegen. Zevenenzestig procent van de mensen die tussen 1989-1993 werd gediagnosticeerd met een indolent B-cel lymfoom, was na vijf jaar nog in leven. Bij patiënten gediagnosticeerd tussen 2004-2007 was dit 75 procent. Voor patiënten met een agressieve vorm van B-cel NHL waren deze percentages respectievelijk 43 en 52 procent. De vijfjaarsoverleving van patiënten met T- en NK-cel lymfomen bleef gelijk in de tijd (48 procent). De verbetering in de overleving van patiënten met een B-cel lymfoom kan waarschijnlijk worden verklaard door de introductie van nieuwe en effectieve medicijnen (met name rituximab) sinds het begin van deze eeuw. Verder kunnen de overlevingskansen zijn verbeterd door betere selectiemethoden, zodat meer patiënten de juiste behandeling krijgen. Daarnaast kunnen meer patiënten de zware chemotherapie tot het einde van de kuur volhouden door toevoeging van ondersteunende behandelingen.

Op basis van gegevens van de Nederlandse kankerregistratie kan worden geconcludeerd dat er steeds meer mensen in Nederland wonen die ooit de diagnose non-Hodgkin lymfoom hebben gehad. Dit komt enerzijds doordat het aantal nieuwe patiënten per jaar is gestegen en anderzijds doordat de overlevingskansen de afgelopen twintig jaar zijn verbeterd. In concrete cijfers: het aantal patiënten met NHL steeg van ongeveer 7.000 in 1992 tot 17.000 in 2007. Dit betekent dat er in 1992 per ziekenhuis gemiddeld 35 patiënten onder behandeling of controle waren. In 2010 is dit aantal opgelopen tot 170 patiënten per ziekenhuis.

In **hoofdstuk 2.2** beschrijven we de relatieve overleving van NHL in verschillende Europese kankerregistraties en in de SEER registratie uit de Verenigde Staten. De relatieve overleving in alle registraties steeg tussen 1990 en 2004 (gemiddeld met 9 procent), maar er bleven verschillen tussen de registraties bestaan. In de Centraal-Europese registraties (Polen, Estland en Letland) steeg de relatieve overleving van patiënten jonger dan 45 jaar zeer sterk. Mede daardoor waren de overlevingspercentages van Centraal-Europa, West-Europa en de Verenigde Staten in de periode 2002-2004 vergelijkbaar. Voor de leeftijdsgroep 45-54 jaar zagen we in

de laatste periode (2002-2004) vergelijkbare overlevingscijfers voor West-Europa en de VS, maar in Centraal-Europa was de overleving lager. Bij patiënten ouder dan 55 jaar was de overleving in de VS hoger dan in alle registraties in Europa. In de leeftijdsgroep 55-64 jaar was 49 procent van de patiënten na vijf jaar nog in leven in Centraal-Europa; in West-Europa was dit 65 procent en in de VS 73 procent. In de leeftijdsgroep 65-74 jaar was dit respectievelijk 31, 55 en 67 procent; en in de oudste leeftijdsgroep (75+) was dit respectievelijk 23, 39 en 52 procent. Mogelijke verklaringen voor deze verschillen in overleving kunnen zijn: verschillen in de zorg (bijvoorbeeld variatie in het gebruik van nieuwe (effectieve) medicijnen, variatie in de ondersteunende zorg of andere richtlijnen), en verschil in de toegang tot zorg en het beschikbare zorgbudget. Verder kan een gedeelte van deze verschillen mogelijk verklaard worden door verschillen in de codering van lymfeklierkanker, verschillen in verdeling van subgroepen of verschillen in registratie van doodsoorzaken.

De verbetering in de overleving van NHL is niet alleen zichtbaar in Nederland, maar ook in Europa en de VS. Verschillende groepen van wetenschappers en artsen (zoals HOVON en EORTC) hebben studies gedaan naar nieuwe behandelingen en ondersteunende zorg voor NHL-patiënten. Dit heeft bijgedragen aan verbetering van de kwaliteit van zorg, maar de verschillen in overleving kunnen erop duiden dat deze verbeteringen niet overal even goed en snel zijn doorgedrongen in de praktijk.

De juiste patiënten selecteren voor behandeling

De overlevingskansen van NHL verschillen sterk van patiënt tot patiënt. Met een prognostische index, waarbij rekening wordt gehouden met persoonlijke kenmerken van de patiënt en de tumor, kan een schatting worden gemaakt van de levensverwachting van een patiënt. Naast een index voor agressief B-cel NHL (het zogenaamde Diffuus Grootcellig B-cel lymfoom) (de International Prognostic Index, IPI) is voor twee verschillende subtypes NHL is een dergelijke index ontwikkeld. De eerste is de 'Follicular Lymphoma International Prognostic Index' (FLIPI) die gericht is op patiënten met een folliculair lymfoom. De tweede is de 'Mantle cell Lymphoma International Prognostic Index' (MIPI) voor patiënten met een mantelcel lymfoom. Zowel de FLIPI als de MIPI zijn ontwikkeld met gegevens van patiënten die meededen aan een klinische trial. Deze trials bevatten nauwelijks oudere patiënten en/of patiënten met bijkomende ziektes. Wij onderzochten de kwaliteit van deze modellen in de alledaagse praktijk in Zuid-Nederland.

De FLIPI bleek redelijk valide. Echter de overleving kon beter worden voorspeld, indien de patiënten specifieker qua leeftijd werden ingedeeld (drie leeftijdsgroepen in plaats van twee) en de aanwezigheid van hart- en vaatziektes werd meegenomen (**hoofdstuk 4.1**). Ook de MIPI bleek valide in de alledaagse praktijk. De MIPI konden we verbeteren door de functionele status (dit is een maat voor de algehele conditie van de patiënt) bij diagnose specifieker te omschrijven (vijf categorieën in plaats van twee). Verder bleek dat het model een betere voorspellende waarde kreeg wanneer de aanwezigheid van bepaalde symptomen en het geslacht werden meegewogen (**hoofdstuk 4.2**). Het is van belang om deze verbeteringen ook te evalueren in andere populaties. Verder is het van groot belang om bij prognostische indexen de achterliggende reden voor een kortere overleving te kennen. Wordt deze veroorzaakt door de ziekte of door de conditie van de patiënt? Deze informatie is van essentieel belang voor het bepalen van de juiste behandeling. Patiënten met een korte levensverwachting worden veelal agressief behandeld om de tumor onder controle te krijgen. Het is echter de vraag of deze keuze altijd terecht is. Immers, agressieve behandelingen gaan vaak gepaard met veel bijwerkingen die de levensverwachting van de patiënt juist kunnen verkorten. Dit probleem doet zich vooral voor bij (fragiele) ouderen en is een uitdaging voor toekomstig onderzoek.

Ouderen

NHL komt vaak voor bij oudere mensen (57 procent van de patiënten is 65 jaar of ouder ten tijde van de diagnose). Door stijgende levensverwachting en lagere geboorteaantallen vindt in Nederland een sterke vergrijzing plaats. Dit heeft geleid tot een stijging van het aantal nieuwe diagnoses van NHL bij ouderen (75+ jaar) (van 880 in 1997 tot 1.309 in 2007). Behandeling van oudere patiënten is vaak complexer en de overleving is slechter. Richtlijnen voor behandeling zijn gebaseerd op klinische studies, waarin ouderen vaak niet worden meegenomen. Het is nog niet bekend of deze richtlijnen ook gelden voor oudere patiënten met NHL. In Nederland bleek slechts 24 procent van de oudere patiënten (75+) met 'stadium I agressief NHL' de standaardcombinatie van chemotherapie en radiotherapie als primaire behandeling te hebben gehad. Ter vergelijking: in de leeftijdsgroep 45-74 jaar was dat 46 procent (**hoofdstuk 5.1**). Daarnaast bleek 65 procent van alle stadium II-IV agressief NHL-patiënten van 75 jaar en ouder chemotherapie als primaire behandeling te krijgen, vergeleken met 89 procent in de leeftijdsgroep 45-74.

In hoofdstuk 5.2 wordt een gedetailleerde beschrijving gegeven van de behandeling van oudere patiënten met NHL. Voor dit onderdeel van de studie hebben we (met instemming van de behandelende artsen) extra informatie verzameld uit de klinische dossiers van 515 patiënten met stadium II-IV agressief B-cel NHL. Er werd informatie verzameld over de precieze behandeling, aanpassingen hiervan, redenen om af te wijken van de standaardbehandeling, bijwerkingen, resultaat van behandeling en overleving. Slechts 27 procent van de patiënten van 75 jaar en ouder kreeg de standaardbehandeling (minimaal zes kuren CHOP-chemotherapie). Geen of suboptimale chemotherapie bleek vaker geassocieerd met patiënten met andere ziekten of een slechte functionele status. Ook vrouwen en patiënten die in een verzorgingstehuis of alleen woonden kregen vaker geen of een suboptimale chemotherapie. Dat gold eveneens voor patiënten met een lage hemoglobine (Hb) waarde in het bloed. De reden om geen chemotherapie te geven, was meestal weigering door patiënt of familie (23 procent), slechte functionele status (19 procent), of een korte levensverwachting (12 procent). Hoge leeftijd was de meest voorkomende reden (26 procent) voor een andere chemotherapie dan CHOP. Achtenzestig procent van de patiënten die CHOP kregen ontwikkelde een of meerdere ernstige bijwerkingen. En bij 76 procent van de patiënten werd de behandeling aangepast (meestal door eerder te stoppen met de behandeling). Het voorspellen van bijwerkingen en tolerantie van CHOP is belangrijk. Mogelijk kan een uitgebreide geriatrische test hierbij uitkomst bieden. De overleving van deze oudere patiënten werd beïnvloed door het stadium bij diagnose, de functionele status, de hoogte van de bloedwaarde LDH en de gegeven behandeling. Leeftijd op zich had dus geen onafhankelijke effect op de overleving bij deze patiënten en zou dus niet voor behandelingsbeslissingen gebruikt moeten worden. Chemotherapie bij oudere patiënten blijft een lastige afweging tussen veel bijwerkingen en de noodzaak tot aanpassingen in de behandeling enerzijds en anderzijds een betere overleving voor degenen die de behandeling kunnen doorstaan.

In dit proefschrift zagen we dat bijkomende ziektes een belangrijke invloed hebben op behandeling en overleving van patiënten met non-Hodgkin lymfoom. In **hoofdstuk 5.3** hebben we in detail gekeken naar patiënten die diabetes hadden naast NHL. Bij deze patiënten werd de behandeling voor NHL vaker aangepast vergeleken met patiënten zonder diabetes, hetgeen leidde tot een lagere dosis van chemotherapie. Patiënten met diabetes kregen tijdens behandeling vaker een te hoog suikergehalte

in het bloed door de hoge dosis steroïde in CHOP-chemotherapie. Na correctie voor verschillen in leeftijd bleek de overleving echter niet slechter voor patiënten met diabetes.

Kortom, oudere patiënten met NHL werden vaak niet of suboptimaal behandeld. Verder zagen we dat zelfs in de selectie van patiënten die voor CHOP in aanmerking kwamen tweederde van alle patiënten ernstige toxiciteit ontwikkelden en dat 41 procent van deze patiënten niet in staat was om de volledige behandeling te voltooien. Patiënten die de behandeling af kunnen maken, hebben echter een verbeterde overleving. Het is daarom belangrijk om te bepalen welke patiënten in staat zijn om de behandeling te ondergaan.

Conclusie

Vergrijzing van de bevolking en een stijging in de incidentie van non-Hodgkin lymfoom hebben geleid tot een toename van het aantal patiënten gediagnosticeerd met NHL. Tegelijkertijd is de overleving verbeterd, mede door verbeteringen in behandeling. De verbetering in overleving werd ook elders in Europa en in de VS waargenomen. Er zijn echter ook regionale verschillen te zien in de overleving, met name bij de oudere patiënt. Deze verschillen kunnen erop duiden dat verbeteringen in zorg niet overal even goed en snel doordringen in de praktijk. Ouderen hebben mogelijk een slechtere overleving, doordat ze minder vaak de standaardbehandeling ontvangen. Van te voren bepalen welke patiënten in staat zijn om de zware chemotherapie voor NHL te ondergaan is zeer belangrijk, omdat het merendeel van de ouderen ernstige bijwerkingen krijgt en daardoor de volledige behandeling niet kan afmaken. Anderzijds moet onderbehandeling van de 'fitte' oudere worden voorkomen, aangezien oudere patiënten die de behandeling kunnen voltooien een duidelijk betere overleving hebben vergeleken met patiënten die geen of suboptimale chemotherapie krijgen.

Curriculum vitae

Curriculum vitae

Saskia van de Schans werd geboren in Nijmegen op 1 oktober 1982. In 2001 behaalde zij het VWO diploma aan het Udens College te Uden. In datzelfde jaar begon ze aan de studie Biomedische Wetenschappen aan de Radboud Universiteit Nijmegen. Tijdens haar hoofdvakstage epidemiologie deed ze onderzoek naar de late effecten van de behandeling van testiskanker (Universitair Medische Centrum Nijmegen, afdeling epidemiologie, prof. Kiemeney). Als bijvakken had ze de onderwerpen infectieziekten en geneesmiddelenonderzoek. In december 2006 studeerde ze af; op dat moment was ze al werkzaam als junioronderzoeker bij het Integraal Kankercentrum Zuid te Eindhoven. Na ongeveer een half jaar onderzoek en een publicatie over COPD bij kanker werd besloten een promotietraject over non-Hodgkin lymfomen in te zetten, met dit proefschrift als eindproduct. Daarnaast werkte ze mee aan projecten over co-morbiditeit bij kankerpatiënten en de conditionele overleving van kankerpatiënten. In juni 2010 is ze bij het Integraal Kankercentrum Oost te Nijmegen in dienst getreden als epidemiologisch onderzoeker.

List of publications

List of publications

In this thesis

1. van de Schans SA, Steyerberg EW, Nijziel MR, Creemers GJ, Janssen-Heijnen ML, van Spronsen DJ: Validation, revision and extension of the Follicular Lymphoma International Prognostic Index (FLIPI) in a population-based setting. Ann Oncol 20:1697-702, 2009
2. van de Schans SA, Janssen-Heijnen ML, Nijziel MR, Steyerberg EW, van Spronsen DJ: Validation, revision and extension of the Mantle cell lymphoma International Prognostic Index (MIPI) in a population-based setting. Haematologica, 2010
3. van de Schans SA, Gondos A, van Spronsen DJ, Rachtan J, Holleczek B, Zanetti R, Coebergh JW, Janssen-Heijnen ML, Brenner H: Improving relative survival, but large remaining differences in survival for non-Hodgkin lymphoma across Europe and the US during 1990-2004., submitted
4. van de Schans SA, Issa D, Visser O, Nooijen P, Huijgens PC, Karim-Kos H, Janssen-Heijnen ML, Coebergh JWW: Diverging trends in incidence and mortality, and improved survival of non-Hodgkin lymphoma, in the Netherlands, 1989-2007 submitted
5. van de Schans SA, van Spronsen DJ, Hooijkaas H, Janssen-Heijnen ML, Coebergh JWW: Excess of Autoimmune and Chronic inflammatory disorders in patients with lymphoma compared with all cancer patients: a cancer registry-based analysis in the south of the Netherlands. submitted
6. van de Schans SA, Wymenga ANW, van Spronsen DJ, Lemmens VEPP, Coebergh JWW, Janssen-Heijnen ML: Two sides of the medallion: poor treatment tolerance, but better survival by chemotherapy in elderly patients with advanced stage aggressive B-cell non-Hodgkin lymphoma. submitted
7. van Herpt TT, van de Schans SA, Haak HR, van Spronsen DJ, Dercksen MW, Janssen-Heijnen ML: The influence of prevalent diabetes mellitus on treatment outcome in non-Hodgkin lymphoma. submitted
8. van de Schans SA, Wymenga ANW, van Spronsen DJ, Lemmens VEPP, Coebergh JWW, Janssen-Heijnen ML: Less standard therapy and poorer survival for senior patients with aggressive B-cell non-Hodgkin lymphoma diagnosed 1997-2007, in the Netherlands. to be submitted

Other publications

9. de Vries E, Houterman S, Janssen-Heijnen ML, Nijsten T, van de Schans SA, Eggermont AM, Coebergh JW: Up-to-date survival estimates and historical trends of cutaneous malignant melanoma in the south-east of The Netherlands. Ann Oncol 18:1110-6, 2007
10. Louwman WJ, Verhoeven RH, van de Schans SA: Cadmium in de Kempen: een statistische analyse van kankerincidenties. Eindhoven, Integraal Kankercentrum Zuid, 2007, pp 1-19
11. van de Poll-Franse LV, van de Schans SA: [Vijfentwintig jaar Integraal Kankercentrum Zuid (IKZ) en meer dan vijftig jaar kankerregistratie: 32.000 kankerpatiënten gediagnosticeerd en behandeld in Máxima Medisch Centrum]. Medisch journaal 36:194-199, 2007

12. van de Schans SA, Janssen-Heijnen ML, Biesma B, Smeenk FW, van de Poll-Franse LV, Seynaeve C, Coebergh JW: COPD in cancer patients: Higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. Eur J Cancer 43:2194-202, 2007

13. van Eycken L, van de Schans SA, Coebergh JW: Klinische epidemiologie van bloed- en lymfeklierkanker in Nederland en Vlaanderen, in Löwenberg B, Ossenkoppele G, de Witte T, et al (eds): Handboek hematologie. Utrecht, de Tijdstroom, 2008, pp 289-312

14. Janssen-Heijnen ML, Szerencsi K, van de Schans SA, Maas HA, Widdershoven JW, Coebergh JW: Cancer patients with cardiovascular disease have survival rates comparable to cancer patients within the age-cohort of 10 years older without cardiovascular morbidity. Crit Rev Oncol Hematol, 2009

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16. van der Schroeff MP, van de Schans SA, Piccirillo JF, Langeveld TP, Baatenburg de Jong RJ, Janssen-Heijnen ML: Conditional relative survival in head and neck squamous cell carcinoma: Permanent excess mortality risk for long-term survivors. Head Neck, 2010

17. Janssen-Heijnen ML, Maas HA, van de Schans SA, Coebergh JW, Groen HJM: Chemotherapy in elderly small-cell lung cancer patients: yes we can, but should we do it? Ann Oncol, in press

18. Janssen-Heijnen ML, van de Schans SA: Epidemiology of geriatric oncology, in Repetto PM- (ed): Geriatric Oncology, in press

19. Olden TE, Schols JM, Hamers JP, van de Schans SA, Coebergh JW, Janssen-Heijnen ML: Predicting the need for improved end-of-life care for elderly cancer patients: findings from a Dutch regional cancer registry database. European Journal of Cancer Care, in press

Acknowledgement

Ackowledgement
Nu het waarschijnlijk meest gelezen gedeelte van mijn proefschrift. Hierin wil ik iedereen bedanken die heeft geholpen om mijn promotie tot een goed einde te brengen en dit proefschrift te maken.

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Daarnaast Maryska Janssen-Heijnen en Dick Johan van Spronsen die als copromotoren altijd klaar stonden voor vragen en advies, meestal zo snel dat ik meteen weer opnieuw aan de slag kon. Maryska bedankt voor je altijd kritische, maar vooral enthousiaste en helpende hand. Misschien leer ik ooit wanneer je "than" ipv "then" moet gebruiken, en dat is dan alleen door hulp van jou. Dick Johan bedankt dat ik met je mee mocht kijken in de praktijk, voor het inzien van de kracht van de kankerregistratie voor de patiëntenzorg en voor de leuke nieuwe ideeën voor onderzoek.

De kleine of ook wel leescommissie, Ewout Steyerberg, Tischa van der Cammen en Peter Sonneveld, wil ik bedanken voor het willen bekijken van mijn proefschrift. Met jullie toestemming weet ik zeker dat het helemaal goed gaat komen tijdens mijn verdediging. De overige leden van mijn promotiecommissie wil ik bedanken voor het lezen van mijn proefschrift en ik kijk uit naar de discussie die we erover zullen gaan voeren.

De stukken in dit proefschrift heb ik natuurlijk niet alleen geschreven, daarom wil ik hier alle overige co-auteurs bedanken: E Steyerberg, M Nijziel, GJ Creemers, A Gondos, J Rachtan, B Holleczek, R Zanetti, H Brenner, D Issa, O Visser, P Nooijen, P Huijgens, H Karim-Kos, H Hooijkaas, A Wymenga, V Lemmens, H Schouten, T van Herpt, H Haak en M Dercksen. Iedereen heeft me vanuit zijn of haar specialisme (patiëntenzorg, hematologie, pathologie, epidemiologie, statistiek) geholpen met het opzetten van de studies, het uitvoeren van de analyses en het schrijven van de

artikelen. Zonder jullie was het onmogelijk. Verder wil ik mevrouw Bieger bedankten voor het corrigeren van de Engelse tekst van de artikelen en de leden van GeriOnNe Onderzoek voor het meedenken over de resultaten van de studie over ouderen met NHL.

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Familie en vrienden wil ik bedanken voor de interesse getoond in mijn onderzoek. Sommige hadden echt geen idee waar ik mee bezig was, maar omdat ik enthousiast was, waren zij dat ook. Misschien dat ze, nu ze dit boekje als resultaat zien, eindelijk weten waar ik al die tijd mee bezig was. Anderen (Inge, Marisa, Milou en mama) hebben me geholpen bij het corrigeren van de teksten en de lay-out van mijn boekje, super bedankt daarvoor. Mijn tweede paranimf Maaike, tijdens onze BMW studie al vaak mijn samenwerkmaatje. We weten elkaar goed in evenwicht te houden en ook tijdens onze promotie konden we lekker ouwehoeren over werk, promotoren, collega's, hobby's en eigenlijk alles.

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PhD portfolio summary

Summary of PhD training and teaching activities

Name PhD student: Saskia van de Schans	PhD period: 2006-2010
Erasmus MC Department: Public Health / Comprehensive Cancer Centre South (Eindhoven)	Promotor(s): Prof. Dr. Jan Willem W. Coebergh
Research School: o. a. NIHES	Supervisor: Dr. Maryska L. G. Janssen-Heijnen & Dr. Dick Johan van Spronsen

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication	2006-2010	40 hours (1.4 ECTS)
- Research Integrity	2006-2010	40 hours (1.4 ECTS)
Research skills		
- Multiple imputation and validation of prognostic models	2006-2010	40 hours (1.4 ECTS)
- Relative survival period analyses, Deutsches Krebsforschungszentrum Heidelberg	2009	40 hours (1.4 ECTS)
In-depth courses (e.g. Research school, Medical Training)		
- "Relative survival: approaches to advanced modelling", Londen School of Hygiene & Tropical Medicine	2007	24 hours (0.9 ECTS)
- "Cancer epidemiology", Netherlands Institute for Health Sciences	2007	40 hours (1.4 ECTS)
- "Subsidie aanvragen" + "Netwerken doe je zo", Nederlandse Organisatie voor Wetenschappelijk Onderzoek	2008	8 hours (0.3 ECTS)
- "Leukemia and lymphoma development – the role of inflammation, autoimmunity and infections", Karolinska Institute Stockholm	2008	32 hours (1.1 ECTS)
- "Leukemia and lymphoma" European School of Oncology	2008	24 hours (0.9 ECTS)
- "Basiscursus oncologie", Nederlandse Vereniging van Oncologie	2009	40 hours (1.4 ECTS)
- "Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen", Erasmus Medical Centre	2009	8 hours (0.3 ECTS)
- "How to print your thesis?" + "Fear & loathing dissertation desert", Erasmus Medical Centre	2009	8 hours (0.3 ECTS)
- "Validating and updating clinical prediction models: is that all we need to improve predictions?" + "Advanced methods to adjust for (un)observed confounding: propensity score methods and sensitivity analyses" Julius Centre	2009	8 hours (0.3 ECTS)
- "Subsidieaanvragen" Werkgroep Epidemiologisch Onderzoek Nederland	2010	4 hours (0.1 ECTS)

Presentations		
- Poster presentation Werkgroep Epidemiologisch Onderzoek Nederland (WEON)	2007	32 hours (1.1 ECTS)
- Oral presentation European Network of Cancer Registries (ENCR)	2007	32 hours (1.1 ECTS)
- Poster presentation International Congress Malignant Lymphoma (ICML)	2008	32 hours (1.1 ECTS)
- Oral presentation Dutch haematology congress (DHC)	2009	32 hours (1.1 ECTS)
- Oral presentation Werkgroep Epidemiologisch Onderzoek Nederland (WEON)	2009	32 hours (1.1 ECTS)
- Poster presentation Sociéte Internationale d'Oncologie Gériatrigue (SIOG)	2009	32 hours (1.1 ECTS)
- Oral presentation Dutch haematology congress (DHC)	2010	32 hours (1.1 ECTS)
- 3x Oral presentation Tumour specific IKZ seminar	2006-2009	96 hours (3.4 ETCS)
- 2x Oral presentation Gerionne seminar	2006-2009	64 hours (2.3 ETCS)
International conferences		
- Dutch and United Kingdom Cancer Registries (UKACR&NCR) meeting	2006	24 hours (0.9 ECTS)
- International Association of Cancer Registries (IACR) conference	2007	32 hours (1.1 ECTS)
- European Network of Cancer Registries (ENCR) conference	2007	8 hours (0.3 ECTS)
- International Congress Malignant Lymphoma (ICML)	2008	32 hours (1.1 ECTS)
- Sociéte Internationale d'Oncologie Gériatrigue (SIOG) conference	2009	24 hours (0.9 ECTS)
Dutch conferences		
- Federatie van medisch wetenschappelijke verenigingen (FEDERA) day	2007	8 hours (0.3 ECTS)
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON) conference	2007	16 hours (0.6 ECTS)
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON) conference	2008	16 hours (0.6 ECTS)
- Federatie van medisch wetenschappelijke verenigingen (FEDERA) day	2008	8 hours (0.3 ECTS)
- Elderly and cancer (Gerionne)	2008	8 hours (0.3 ECTS)
- Dutch haematology congress (DHC)	2009	16 hours (0.6 ECTS)
- Nederlandse Vereniging voor Oncologie (NVvO) day	2009	8 hours (0.3 ECTS)
- Vereniging Integrale Kanker Centra (VIKC) research day	2009	8 hours (0.3 ECTS)
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON) conference	2009	16 hours (0.6 ECTS)
- Elderly and cancer (Gerionne)	2009	8 hours (0.3 ECTS)
- Dutch haematology congress (DHC)	2010	8 hours (0.3 ECTS)
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON) conference	2010	16 hours (0.6 ECTS)

Seminars and workshops		
- VIKC seminar series	2006-2010	6x3=18 hours (0.6 ECTS)
- Tumour specific IKZ seminar series (“tumor werkgroepen”)	2006-2010	10x2=20 hours (0.7 ECTS)
- Theme specific IKZ seminar series (“thema avonden”)	2006-2009	4x3=12 hours (0.4 ECTS)
- Statistical IKZ seminars	2006-2009	7x1=7 hours (0.3 ECTS)
- Statistical EMC seminars	2006-2010	3x2=6 hours (0.2 ECTS)
- Gerionne seminars	2006-2010	5x2=10 hours (0.4 ECTS)
- Seminar UMCN epidemiology	2008	1x2=2 hours (0.1 ECTS)
Other		
- Literature research	2009	100 hours (3.6 ECTS)
- Data analyses on survival	2006-2010	160 hours (5.7 ECTS)
- Data analyses on co-morbidities	2006-2010	160 hours (5.7 ECTS)
2. Teaching activities		
	Year	**Workload (Hours/ ECTS)**
Supervising Master’s theses		
- 2 Master students Maastricht university (T v Herpt and M v Waalwijk)	2008-2010	80 hours (2.9 ECTS)
- 1 Master student Nijmegen university (K Szerenci)	2009	40 hours (1.4 ECTS)
Total		1611 (57.5 ECTS)