Trends in incidence, treatment and survival of aggressive B-cell lymphoma in the Netherlands 1989-2010

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ABSTRACT

Only a small number of patients with aggressive B-cell lymphoma take part in clinical trials, and elderly patients in particular are under-represented. Therefore, we studied data of the population-based nationwide Netherlands Cancer Registry to determine trends in incidence, treatment and survival in an unselected patient population. We included all patients aged 15 years and older with newly diagnosed diffuse large B-cell lymphoma or Burkitt lymphoma in the period 1989-2010 and mantle cell lymphoma in the period 2001-2010, with follow up until February 2013. We examined incidence, first-line treatment and survival. We calculated annual percentage of change in incidence and carried out relative survival analyses. Incidence remained stable for diffuse large B-cell lymphoma (n=23,527), while for mantle cell lymphoma (n=1,634) and Burkitt lymphoma (n=724) incidence increased for men and remained stable for women. No increase in survival for patients with aggressive B-cell lymphoma was observed during the period 1989-1993 and the period 1994-1998 [5-year relative survival 42% (95%CI: 39%-45%) and 41% (38%-44%), respectively], but increased to 46% (43%-48%) in the period 1999-2004 and to 58% (56%-61%) in the period 2005-2010. The increase in survival was most prominent in patients under 65 years of age, while there was a smaller increase in patients over 75 years of age. However, when untreated patients were excluded, patients over 75 years of age had a similar increase in survival to younger patients. In the Netherlands, survival for patients with aggressive B-cell lymphoma increased over time, particularly in younger patients, but also in elderly patients when treatment had been initiated. The improvement in survival coincided with the introduction of rituximab therapy and stem cell transplantation into clinical practice.

Introduction

Randomized clinical trials of aggressive non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and Burkitt lymphoma (BL), show considerable improvement in clinical outcome over the last two decades. First, the introduction in 1997 of the monoclonal antibody targeting CD20, rituximab, increased overall survival (OS).[1-4] Second, the introduction of more intensive therapy in first-line treatment, including autologous stem cell transplantation (ASCT), improved OS of MCL and BL.[5-9]

However, only a small selection of patients taken from the entire patient population typically takes part in randomized clinical trials. Particularly patients with comorbidities and age-related organ dysfunction are under-represented in clinical trials.[10] Moreover, patients aged 80 years or older are often excluded from trials.[3,11] This situation highlights the importance of population-based registries that provide the opportunity to determine whether new treatment options are implemented and whether this is beneficial in an unselected patient population, including elderly patients or patients with marked comorbidity.

Several existing population-based registries on the clinical outcome in aggressive B-cell lymphoma show an improvement in survival.[12-14] However, this is the first large population-based study with separate analyses of specific pathological subtypes of aggressive B-cell lymphoma in different age groups, with regard to incidence and survival over time.

Methods

Study population and data collection

The Netherlands Cancer Registry (NCR) started in 1989 and is based on notification of all newly diagnosed malignancies in the Netherlands by the automated national pathological archive PALGA. Information on patients' characteristics, tumor characteristics, and primary treatment are routinely obtained from medical records.

Information on the date of death (date of last follow up: February 1st, 2013) was actively obtained from the municipal registries (GBA) and from the database of deceased persons of the Central Bureau for Genealogy. Survival time was calculated as time from date of diagnosis to date of death, date of emigration or to February 1st, 2013.

For the present study, all newly diagnosed patients over 15 years of age were selected with DLBCL (ICD-O-3 morphology codes: 9680, 9684, 9675, 9679, 9591, 9590; ICD-O-2: 9593, 9677, 9681, 9682, 9712), BL (ICD-O-3: 9687, 9826) in the period 1989-2010, and MCL (ICD-O-3: 9673) in the period 2001-2010 (from 2001, MCL was a separate diagnosis).

As the survival pattern (a high number of deaths in the first year after diagnosis) of unspecified NHL was roughly the same as for DLBCL or BL, unspecified NHL (decreasing from 18% in the period 1989-1993 to 6% in the period 2005-2010) was considered as aggres-

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sive lymphoma and classified as DLBCL (since 84% of aggressive lymphoma is DLBCL) for the incidence analyses. This was done to minimize the effect of changes in classification on outcome of trends analyses of incidence. For the survival analyses, we excluded the unspecified cases.

Year of diagnosis was divided into four periods for DLBCL and BL: 1989-1993, 1994-1998, 1999-2004, and 2005-2010, and into two periods for MCL: 2001-2004 and 2005-2010.

Treatment

Primary treatment was described as percentage of patients who received chemotherapy alone, radiotherapy alone, chemotherapy+radiotherapy, transplantation (+/-radiotherapy/chemotherapy), other therapies, no therapy, and unknown therapy, for subgroup, stage, age group and period. Complete data on the use of immunotherapy have been registered by the NCR since 2007.

Statistical analyses

Annual incidence rates according to sex for the period 1989-

Table 1. Patients' characteristics of aggressive B-cell lymphoma, according to subgroup, in the Netherlands, 1989-2010.

		DLBCL	MCL	BL
N		23527	1634	724
Mean age (range) (yr)		66 (15-103)	71 (28-93)	49 (15-93)
Age (%)	15-39	7	2	35
	40-64	33	33	37
	65-74	26	33	14
	>75	34	32	14
Male sex (%)		53	74	66
Stage (%)	I	27	6	18
	II	20	9	13
	III	16	13	9
	IV	30	70	55
	Unknown	7	2	5

DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; BL: Burkitt lymphoma.

Table 2. Overview of clinical trials of aggressive B-cell lymphoma; OS compared with outcome in the Netherlands.

Study	Regimen	Median age/range	Patients number	OS (%) CI (%)	Median age/range	Patients number	OS (%) CI (%) 2001-2010; all cases	Patients number	OS (%) CI (%) 2001-2010; only CT cases
	Clinical studies				Our study				
DLBCL									
Pfreundschuh *et al.*[3]	6 CHOP14	68 (61-80)	1,222	68 (62-74) at 3 yrs	72 (61-80)	5,408	54 (53-55)	4,504	61 (60-63)
	8 CHOP14			66 (60-72) at 3 yrs			at 3 yrs		at 3 yrs
	6 R-CHOP14			78 (73-83) at 3 yrs					
	8 R-CHOP14			73 (67-78) at 3 yrs					
Feugier *et al.* (2005)[11]	R-CHOP21	69 (60-80)	399	58 (51-65) at 5 yrs	71 (60-80)	5,610	46 (45-48)	4,684	53 (51-54)
Coiffier *et al.* (2010)[15]	CHOP21			45 (39-53) at 5 yrs			at 5 yrs		at 5 yrs
				44 (36-54) at 10 yrs			30 (29-33)		35 (33-37)
				28 (21-34) at 10 yrs			at 10 yrs		at 10 yrs
Pfreundschuh *et al.*[16]	R-CHOP like	47 (35-55)	823	90 (86-93) at 6 yrs	48 (35-55)	1,954	71 (69-73)	1,848	73 (71-75)
	CHOP like			80 (75-84) at 6 yrs			at 6 yrs		at 6 yrs
Ohmachi *et al.*[17]	CHOP14	57 (17-69)	323	55 (47-63) at 8 yrs	58	5,566	60 (59-62)	5,158	63 (61-64)
	CHOP21			56 (47-64 at 8 yrs	(17-69)		at 8 yrs		at 8 yrs
Recher *et al.*[18]	R-ACVBP	48 (18-59)	379	92 (87-95) at 3 yrs	49	3,209	75 (74-77)	3,025	77 (76-79)
	R-CHOP			84 (77-89) at 3 yrs	(18-59)		at 3 yrs		at 3 yrs
Peyrade *et al.*[19]	6 R-miniCHOP	83 (80-95)	150	59 (49-67) at 2 yrs	84	2,134	30 (28-32)	1,030	45 (42-48)
					(80-95)		at 2 yrs		at 2 yrs
Cunningham *et al.*[20]	6R-CHOP14 + 2R	61 (19-88)	1080	83 (80-86) at 2 yrs	69 (19-88)	10,323	60 (59-61)	8,453	69 (68-70)
	8 R-CHOP21			81 (78-84) at 2 yrs			at 2 yrs		at 2 yrs
Delarue *et al.*[21]	8 R-CHOP14	70 (59-80)	602	69 (64-72) at 3 yrs	71 (59-80)	5,805	55 (54-56)	4,860	62 (61-64)
	8 R-CHOP21			72 (67-77) at 3 yrs			at 3 yrs		at 3 yrs
MCL									
Van 't Veer *et al.*[22]	R-CHOP, HD Ara-C,	55 (32-66)	87	79 at 4 yrs	58 (32-66)	602	62 (58-66)	536	62 (58-66)
	BEAM-ASCT						at 4 yrs		at 4 yrs
Damon *et al.*[23]	R-M-CHOP+	57 (37-69)	79	64 at 5 yrs	61 (37-69)	738	54 (50-58)	650	54 (49-58)
	EAR+CBV-ASCT						at 5 yrs		at 5 yrs
Gressin *et al.*[24]	8VAD+C	> 60 (61-75)	35	51 at 3 yrs	69 (61-75)	747	52 (48-55) at 3 yrs	621	52 (48-56) at 3 yrs
	6(R)VAD+C+ASCT	< 65 (18-64)	78	67 at 3 yrs	57 (18-64)	517	72 (68-76) at 3 yrs	462	73 (68-77) at 3 yrs
Romaguera *et al.*[25]	R-HCVAD-AM	61 (41-80)	97	56 at 8 yrs	69 (41-80)	1,366	29 (26-32) at 8 yrs	1,123	29 (26-32)at 8 yrs
	Age ≤65 years		65	68 at 8 yrs			≤65 47 (42-52) at 8 yrs		≤65 47 (41-52) at 8 yrs
	Age >65 years		32	33 at 8 yrs			>65 17 (14-20) at 8 yrs		>65 16 (13-20) at 8 yrs
Merli *et al.*[26]	R-HCVAD-AM	57 (22-66)	60	73 (59-83) at 5 yrs	58 (22-66)	603	58 (53-62) at 5 yrs	536	57 (53-61) at 5 yrs
Geisler *et al.*[8]	R-maxiCHOP+R-	56 (32-65)	160	66 at 6 yrs	58 (32-65)	557	50 (45-54) at 6 yrs	495	49 (44-54) at 6 yrs

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2010 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 (ASR). Incidence rates were also calculated per age group. Trends in incidence were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (95%CI).

Relative survival (RS), which can be interpreted as disease-specific survival within a cancer patient population (independent of the cause of death), was estimated as ratio of the observed survival of cancer patients and the expected survival of a comparable age- and sex-matched group of the general population.

In order to compare results with those from recent clinical studies we also calculated OS. For each phase II or III study with a minimum number of cases (DLBCL 140, MCL 60, BL no minimum) published since 2008 (DLBCL, MCL) or 2005 (BL), we selected patients from the NCR with the same age range and same diagnosis as patients in the equivalent trial. OS was calculated for all patients as well as for patients receiving chemotherapy with the same age range and diagnosis for the period 2001-2010.

Table 2. (continued from previous page)

Study	Regimen	Median age/range	Patients number	OS (%) CI (%)	Median age/range	Patients number	OS (%) CI (%) 2001-2010; all cases	Patients number	OS (%) CI (%) 2001-2010; only CT cases
	Clinical studies				Our study				
Geisler *et al.*[27]	HD Ara-C+BEAM/BEAC- ASCT			58 at 10 yrs			37 (30-43) at 10 yrs		36 (29-43) at 10 yrs
Raty *et al.*[28]		74 (65-83)	60	72 at 4 yrs	74 (65-83)	980	34 (31-37) at 4 yrs	786	34 (30-37) at 4 yrs
Kluin-Nelemans *et al.*[29]	R-FC	70 (60-83)	560	47 at 4 yrs	72 (60-83)	1,157	38 (35-41) at 4 yrs	906	38 (35-41) at 4 yrs
	R-CHOP			62 at 4 yrs					
	R-CHOP+ MT R			87 at 4 yrs					
	R-CHOP+ intα			63 at 4 yrs					
Delarue *et al.*[5]	CHOP, DHAP +R, BEAM-ASCT	57 (40-66)	60	75 at 5 yrs BL	59 (40-66)	589	57 (53-61) at 5 yrs	526	56 (52-61) at 5 yrs
BL									
Divine *et al.*[30]	LMB protocol	33 (18-76)	72	70 at 2 yrs	46 (18-76)	332	51 (46-57) at 2 yrs	291	57 (61-63) at 2 yrs
	Age <33 years		37	84 at 2 yrs			<33 73 (61-81) at 2 yrs		<33 74 (62-82) at 2 yrs
	Age ≥33 years		35	60 at 2 yrs			≥33 46 (39-51) at 2 yrs		≥33 52 (45-58) at 2 yrs
Van Imhoff *et al.*[9]	HD sequential CT+ ASCT	36 (15-64)	27	81 at 5 yrs	41 (15-64)	274	57 (51-63) at 5 yrs	257	59 (53-65) at 5 yrs
Thomas *et al.*[4]	R-Hyper-CVAD	46 (27-77)	31	89 at 3 yrs	50 (27-77)	291	46 (40-52) at 3 yrs	248	52 (46-58) at 3 yrs
	Age < 60 years		22	90 at 3 yrs			<60 56 (48-63) at 3 yrs		<60 58 (50-65) at 3 yrs
	Age ≥ 60 years		9	89 at 3 yrs			≥60 28 (19-37) at 3 yrs		≥60 39 (28-50) at 3 yrs
Hoelzer *et al.*[31]	GMALL B-ALL/NHL	15-55	115	91 at 3 yrs	38 (15-55)	228	64 (57-70) at 3 yrs	214	66 (60-72) at 3 yrs
		≥ 55 (56-78)	36	84 at 3 yrs	68 (56-78)	128	30 (23-39) at 3 yrs	96	41 (31-50) at 3 yrs
Mead *et al.*[32]	dm CODOX-M/IVAC	37 (17-76)	53	67 (54-80) at 2 yrs	45 (17-76)	334	52 (46-57) at 2 yrs	293	58 (52-63) at 2 yrs
Oriol *et al.*[33]	GMALL B-ALL/NHL	36 (15-55)	36	77 (64-90) at 2 yrs	38 (15-55)	228	64 (58-70) at 2 yrs	214	67 (60-73) at 2 yrs
Rizzieri *et al.*[34]	CALGB 10002	(19-79)	105	79 at 2 yrs	47 (19-79)	342	50 (44-55) at 2 yrs	291	57 (51-62) at 2 yrs
Dunleavy *et al*[35]	DA-EPOCH-R	35 (16-88)	30	82 at 4 yrs	49 (16-88)	376	47 (42-52) at 4 yrs	311	55 (49-60) at 4 yrs
Corazzelli *et al.*[36]	dm CODOX-M/IVAC	52 (25-77)	30	82 at 4 yrs	50 (25-77)	293	45 (39-51) at 4 yrs	249	52 (45-58) at 4 yrs
	age <60 years		18						
	age ≥60 years		12						
Hoelzer *et al.*[37]	Short-intensive CT		363			371		309	
	B-NHL	40 (16-79)		88 at >7 yrs	46 (16-79)		52 (46-58) at 7 yrs		59 (52-65) at 7 yrs
	Age 15-≤25 years			91 at >7 yrs			83 (67-91) at 7 yrs		85 (69-93) at 7 yrs
	Age 26-55 years			91 at >7 yrs			60 (52-68) at 7 yrs		63 (54-70) at 7 yrs
	Age >55 years			80 at >7 yrs			28 (19-38) at 7 yrs		38 (26-50) at 7 yrs
	B-L	47 (16-85)			53 (18-82)				
	Age 15-≤25 years			90 at >7 yrs			70 (33-89) at 7 yrs		70 (33-89) at 7 yrs
	Age 26-55 years			71 at >7 yrs			36 (18-54) at 7 yrs		37 (19-55) at 7 yrs
	Age >55 years			46 at >7 yrs			9 (2-22) at 7 yrs		13 (3-30) at 7 yrs
Kasamon *et al.*[38]	BASIC therapy	53 (34-75)	21	57 (40-83) at 3 yrs	52 (34-75)	242	44 (37-50) at 3 yrs	207	50 (43-56) at 3 yrs

OS: overall survival; yrs, years; CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednison; R: rituximab; R-ACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; HD Ara-C: high dose cytarabine; BEAM: carmustine, etoposide, Ara-C, melphalan; ASCT: autologous stem cell transplantation; M: methotrexate; EAR: etoposide, cytarabine, rituximab; CBV: carmustine, etoposide, cyclophosphamide;VAD: vincristine, doxorubicine, dexamethasone; C: chlorambucil;R-HCVAD-AM: rituximab-hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone)-high dose cytararabine, methotrexate; MT: maintenance therapy; F: fludarabine; FC: fludarabine, cyclophosfamide; int α, interferon alfa; DHAP: dexamethasone, high-dose cytarabine, cisplatin; HD: high dose; CT: chemotherapy; dm CODOX-M/IVAC: dose-modified cyclophosphamide, cytarabine, doxorubicin, leucovorin, methotrexate, vincristine/cytarabine, etoposide, ifosfamide, methotrexate; DA-EPOCH-R; B-NHL: Burkitt Non-Hodgkin lymphoma; B-L: Burkitt leukemia; BASIC: brief, anthracycline-sparing, intensive cyclophosphamide.

Statistical analyses were carried out using SAS software (SAS system 9.2; SAS Institute, Cary, NC, USA).

Results

Demographic data

Table 1 shows the demographic data of patients with newly diagnosed DLBCL, MCL and BL in the Netherlands during the period 1989-2010. Mean age of patients with Burkitt lymphoma was considerably lower than DLBCL and MCL (49, 66 and 71 years, respectively). There was a strong male predominance for MCL and BL, 74% and 66%, respectively, which was not observed in DLBCL patients (53%). Stage IV disease was more pronounced in MCL and BL (70 and 55%, respectively) *versus* 30% in DLBCL.

Trends in incidence

Age-standardized incidence (ASR) per 100,000 person-years remained stable for DLBCL (7.7 in 1989, 7.6 in 2010 for men (EAPC -0.3%, 95%CI: -0.4-0.1%), and 5.2 in 1989 [5.0 in 2010 for women (EAPC -0.4%, 95%CI: -0.7- -0.1%)] (Figure 1). Little change was observed in age-specific rates (Figure 2A).

For patients with MCL, there was no significant change in ASR between 2001 and 2010, in males (ASR 1.3 in 2001 and 1.4 in 2010) or in females (ASR 0.4 in 2001 and in 2010) (Figure 1). Stratified by age, we found a large increase in MCL patients over 75 years of age (EAPC males +5.4%, 95%CI: 1.3%-9.6%; females +8.3% 95%CI: -2.1%-20%). However, the increase was statistically significant in males only (Figure 2B).

The ASR of BL increased from 0.2 in 1989 to 0.4 in 2010 for men (EAPC 3.2%, 95%CI: 1.6-4.7) and remained stable for women [0.1 in 1989 and 2010 (EAPC 1.4%, 95%CI: -1.4-4.2)].

Trends in first-line treatment

DLBCL: the majority of patients with DLBCL (56%) received "chemotherapy alone", in particular for stage II, III and IV. The percentage of patients with stage I who received "radiotherapy alone" decreased over time (from 33% to 10%), whereas the percentage of patients who received combination "chemotherapy plus radiotherapy" increased (from 18% to 37%) (Figure 3A).

A considerable proportion of elderly patients did not receive any treatment (17% in patients 65-74 years of age and 36% in patients ≥75 years, *vs.* only 10% in patients <65 years).

Data on treatment with rituximab have been available since 2007. The percentage of patients receiving immunochemotherapy rose from 83% in 2007 to 97% in 2010, independent of age.

Furthermore, patients with DLBCL were generally not treated with stem cell transplantation as first-line treatment.

MCL: the majority of patients with MCL (62%) received "chemotherapy alone", in particular for stage II, III and IV.

A considerable proportion of elderly patients did not receive any treatment (16% in patients 65-74 and 34% in patients ≥75 years *vs.* only 10% in patients <65 years).

During 2007-2010, the percentage of patients treated with rituximab (in combination with chemotherapy) rose over time, from 68% in 2007 to 90% in 2010. However, the proportion of patients treated with rituximab in 2010 was considerably higher in patients aged under 65 years of years and aged 65-74 years, (98% and 94%, respectively) than in patients over 75 years of age (78%; χ^2 test: P=0.004). Moreover, stem cell transplantation was administered more to patients with MCL under 65 years of age, rising from 18% in the period 2001-2004 to 50% in the period 2005-2010 (Figure 3B).

BL: the majority of patients with BL (61%) received "chemotherapy alone" without any distinction in stage (Figure 3C). The percentage of patients receiving no treatment was considerably higher in patients aged > 65 years than in patients aged 40-64 years and <40 years (38%, 10% and 4%, respectively). The percentage of patients treated with rituximab (in combination with chemotherapy) rose over time, from 65% in 2007 to 88% in 2010, independent of age.

Furthermore, the percentage of patients with BL under 65 years of age receiving stem cell transplantation, increased from 5% in the period 1989-1993 to 18% in the period 2005-2010.

Trends in survival

In the first ten years of the study period (1989-1998), no increase in survival of aggressive B-cell lymphoma was observed [5-year RS 42% (95%CI: 39%-45%) and 41% (95%CI: 38%-44%) in 1989-1993 and 1994-1998, respectively]. After 1998, relative survival rose [5-year RS 46% (95%CI: 43-48%) in 1999-2004], particularly since 2005 (5-year RS 58%, 95%CI: 56%-61%).

DLBCL: the 5-year RS for patients with DLBCL under 65 years of age increased remarkably with 28%, from 57% (95%CI: 54%-59%) in the period 1989-1993 to 75% (95%CI: 73%-77%) in the period 2005-2010. Relative survival for patients aged 65-74 years rose by 22%, from 40% (95%CI: 36%-43%) in the period 1989-1993 to 62% (95%CI: 59%-64%) in the period 2005-2010. For patients over 75 years of age, survival increased by 13%, from 28% (95%CI: 24-32%) in the period 1989-1993 to 41% (95% CI 38-44%) in the period 2005-2010 (Figure 4A). After exclusion of untreated patients, results for patients under 75 years of age were the same. However, patients over 75 years of age showed a remarkable rise in survival of 20%, from 33% (95%CI: 29-38%) in the period 1989-1993 to 53% (95%CI: 49%-57%) in 2005-2010 (data not shown). Sex did not significantly affect these results. Furthermore, as expected, outcome deteriorated with increased disease stage, with a 5-year RS ranging from 72% for stage I to 42% for stage IV in the period 2005-2010.

MCL: the 5-year RS for patients with MCL aged under 65 years of age increased remarkably (by 20%), from 52% (95%CI: 44%-60%) in the period 2001-2004 to 72% (95%CI: 66%-77%) in the period 2005-2010.

The RS increased with 18% for patients 65-74 years, from 24% (95%CI: 19%-30%) in the period 2001-2004 to 42% (95%CI: 36%-49%) in the period 2005-2010. For patients over 75 years of age the survival increased with 11%, from 17% (95%CI: 11%-23%) to 28% (95%CI: 22%-35%).

The difference in 5-year survival for all patients with MCL under 65 years of age treated with and without a stem cell transplantation was significant, 77% and 48% respectively (P<0.0001) (*data not shown*). No difference in survival was observed when untreated patients were excluded. Sex did not significantly affect these results.

Furthermore, outcome was inferior with increased disease stage, with a 5-year RS ranging from 67% for stage I to 41% for stage IV in the period 2005-2010.

BL: for patients with BL under 40 years of age, 5-year RS increased by 30%, from 44% (95%CI: 28%-58%) in the period 1989-1993 to 74% (95%CI: 63%-82%) in the period 2005-2010. The survival for patients aged 40-64 years rose by 16%, from 32% (95%CI: 18%-47%) in 1989-1993 to 48% (95%CI: 37%-58%) in the period 2005-2010. Relative survival for patients over 65 years of age increased by less than 10%, from 18% (95%CI: 6%-38%) in the period 1989-1993 to 28% (95%CI: 17%-41%) in the period 2005-2010 (Figure 4C). When untreated patients were excluded, the results for patients under 65 years of age were the same, in contrast to patients over 65 years of age who showed a rise in survival of 15%, from 26% (95%CI: 8%-51%) in the period 1989-1993 to 41% (95%CI: 25%-59%) in the period 2005-2010 (*data not shown*). However, these data were not statistically significant. Sex did not significantly affect these results.

Table 2 shows a comparison of OS from our study with that reported in recent clinical trials, with the same age range and same diagnosis as patients in the equivalent trial. Our study showed inferior survival rates for patients with DLBCL, MCL and BL, even when untreated patients were excluded.

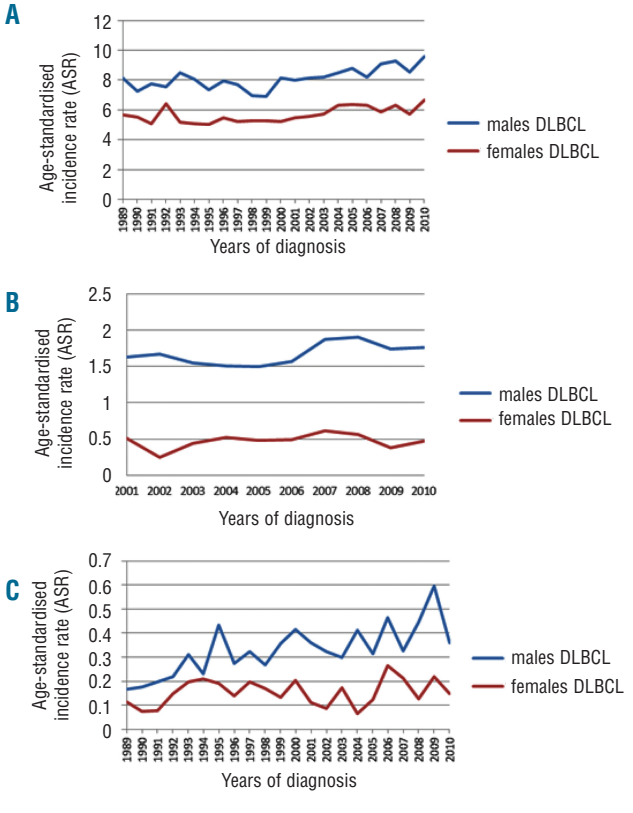

Figure 1. (A). Age-standardized incidence rate (ASR) of diffuse large B-cell lymphoma (DLBCL), according to subgroup and sex, in the Netherlands, 1989-2010. (B). Age-standardized incidence rate (ASR) of mantle cell lymphoma (MCL), according to subgroup and sex, in the Netherlands, 2001-2010. (C). Age-standardized incidence rate (ASR) of BL, according to subgroup and sex, in the Netherlands, 1989-2010.

Discussion

Our population-based registry showed similar incidence rates to those found in other studies conducted in Europe, in particular, a similar increase in incidence of male patients with MCL and BL.[39-41] The causes for male predominance in MCL and BL are still unknown.[42-44]

Furthermore, our study showed a pronounced improvement in survival for patients with aggressive B-cell lymphoma, particularly during the last decade. Although the improvement in survival was observed independent of age, the outcome was significantly inferior in the elderly patients, especially in patients over 75 years of age. Compared with previous population-based studies in Europe and the United States, our study showed similar RS for patients with aggressive B-cell lymphoma.[45-48] For example, in the period 1973-2003, the SEER (Surveillance, Epidemiology and End Results) database showed a RS of 48% for DLBCL, 53% for MCL and 45% for BL.[47] In the period 2000-2002, the European database showed an RS of 49% for DLBCL, 44% for MCL and 56% for BL.[45] The Swedish Lymphoma Registry showed a similar improvement in survival for MCL: an increase in 3-year OS from 47% in the period 2000-2005 to 62% in the period 2006-2010.[49] However, compared with clinical trials, our study showed inferior survival rates for patients with DLBCL, MCL and BL, even when the same age range was analyzed and when untreated patients were excluded (Table 2). The discrepancy in survival in patients under and patients over 65 years of age was comparable among clinical trials and our study.

As our population-based data are not randomized, comparison of DLBCL treated with CHOP with or without rit-

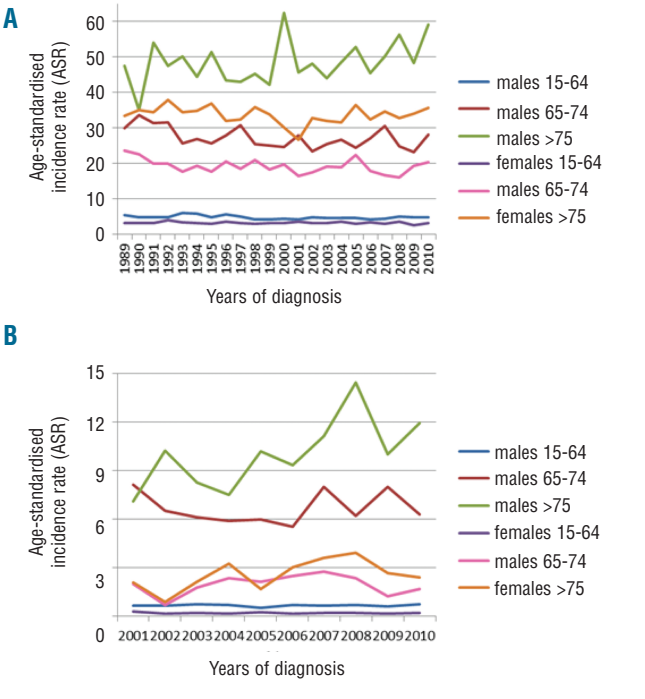

Figure 2. (A). Age-standardized incidence rate (ASR) of diffuse large B-cell lymphoma (DLBCL), by sex and age, in the Netherlands, 1989-2010. (B). Age-standardized incidence rate (ASR) of mantle cell lymphoma (MCL), by sex and age, in the Netherlands, 2001-2010.

uximab should be interpreted with caution. However, as expected, stratified by age group, we found an absolute difference in 5-year survival of approximately 20% in favor of rituximab. Bias in patient selection is likely to have contributed to this large difference.

There are several explanations for the difference in survival between young and elderly patients and the inferior outcome in our study compared with clinical trials. First, only a small, selected proportion of the entire patient population takes part in trials; in particular, elderly patients and those with serious comorbidity are under-represented[50,51] and patients aged 80 years or older are often excluded. [5,15,52-54] Since age is a strong adverse prognostic factor in aggressive B-cell lymphoma, exclusion of elderly patients results in higher survival rates in trials.[10,55,56] For example, Advani showed that patients aged 70 years or over were at increased risk of failure compared to patients under 70 years of age, with a 3-year OS of 58% [95%CI: (49, 66)] and 74% [95%CI: (72, 82)], respectively.[56] Furthermore, comorbidity has been found to be related to age. In the study of Janssen-Heijnen, 79% of patients over 60 years of age diagnosed with NHL had serious comorbidity in contrast to only 48% for patients under 60 years of age.[57] Besides, in the presence of comorbidity, the percentage of patients receiving chemotherapy declined, especially among elderly patients.[58] This is supported by the significantly higher proportion of elderly patients in our study compared to clinical trials, with a mean age of 66 years in our study *versus* 61 years in the study of Cunningham.[20] A considerable number of the elderly patients in our study did not receive any treatment and consequently they had a low survival rate. However, even after correcting for non-treatment, survival remains inferior when compared with clinical trials.

Differences in therapy could be a second reason. For example, rituximab came into use in the USA in 1997 and in Europe in 2000, albeit not simultaneously in all countries.[59,60] This is reflected by the consistently observed higher OS in the rituximab treated patients in the randomized clinical trials, as described in Table 2. Besides, in general a delay in the introduction of new agents is observed in the elderly population with comorbidity. For example, elderly patients with MCL in our study received less treatment with rituximab than younger patients.

A further explanation is that, in general, elderly patients did not receive intensive chemotherapy combined with autologous stem cell transplantation, whereas a high percentage of the younger patients did. In our study, this is seen in particular for MCL patients: patients under 65 years of age were treated with a stem cell transplantation in 50% of the cases compared with 1% in patients over 65 years of age.

Several studies have reported that elderly patients, aged up to 80 years, are able to tolerate full-dose R-CHOP reg-

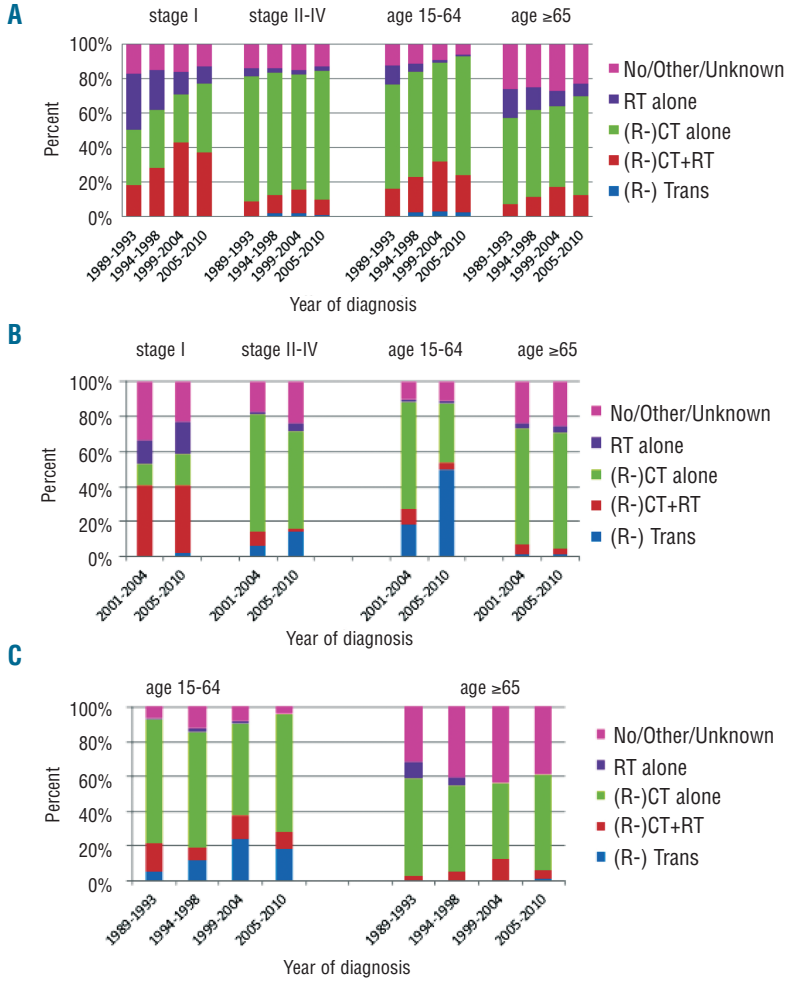

Figure 3. (A). Trends in primary treatment for diffuse large B-cell lymphoma (DLBCL), according to period, stage and age, in the Netherlands, 1989-2010. (B). Trends in primary treatment for mantle cell lymphoma (MCL), according to period, stage and age, in the Netherlands, 2001-2010. (C). Trends in primary treatment for Burkitt lymphoma (BL), according to period and age, in the Netherlands, 1989-2010.

imens.[3,5,20] Although approximately one-third of the cases of NHL occur in patients older than 75 years, few data are available concerning the optimal treatment in this age group. It has been assumed that many older patients are too frail to receive standard therapy.[10,61] Peyrade showed in very elderly patients aged over 80 years, that addition of rituximab to 50%-reduced CHOP seems to be a good compromise between toxicity and efficacy, with a 2-year OS of 59%.[19] Although no precise data on the dose of therapy are available, also in our study, good results were observed for elderly patients receiving treatment , with a 2-year OS of 45% for cases diagnosed in the period 2001-2010.

This study has several limitations, which must be considered when interpreting our results.

First, the classification of aggressive lymphoma has changed considerably over time, with a decrease in the number of unspecified cases. These unspecified cases might have been incorrectly diagnosed as DLBCL, as this is by far the largest diagnostic group of the aggressive lymphomas. Part of the unspecified cases may actually have been MCL, BL or indolent lymphoma. However, the equivalent survival curves of unspecified and aggressive lymphoma support our classification strategy, with only a 1% difference in survival between both groups, implying that this percentage does not generally affect the analyses.

Second, the classification criteria for BL have changed over time, which may have influenced the results for BL. Moreover, during the period 1989-1992, Burkitt leukemia could not be included as in that period no separate morphology code was available in the International Classification of Diseases for Oncology (ICD-O). Consequently, the observed incidence rate for BL during the period 1989-1992 is slightly under-estimated.

Third, despite the rather clinical nature of the Dutch cancer registries, the lack of detailed information regarding exact treatments, comorbidities and dose adherence in our population-based registry has limited the possibility of exploring and clarifying specific reasons for the observed changes in survival.

In conclusion, in the Netherlands, survival for newly diagnosed patients with aggressive B-cell lymphoma has increased over time, particularly in patients under 65 years of age. However, even though survival of elderly patients was inferior in comparison with survival of younger patients, a similar increase in survival occurred when treatment was initiated.

The main contributors to the improvement in survival in our study and clinical trials appear to be rituximab therapy,[1-4,31,59,62,63] autologous stem cell transplantation, and the use of more intensive chemotherapy.[5-9,22,64,65]

The therapeutic goal in treating elderly NHL patients must be to maintain a balance between effective therapy and treatment toxicity. As patients over 65 years constitute around two- thirds of all patients with aggressive lymphoma, clinical trials for elderly 'frail' patients with no barrier for comorbidity are needed to determine appropriate therapy for these patients. Comprehensive geriatric assessment (CGA) could be used for additional information.[66,67]

Since it is important to have more detailed information regarding exact treatments, dose adherence and comorbidities for a better understanding of the treatment and outcome of patients with hematologic malignancies, an extensive registry was initiated in the Netherlands, supplementary to the cancer registry. This PHAROS registry (Population-based Haematological Registry for Observational Studies) is expected to supply more detailed data in the near future.

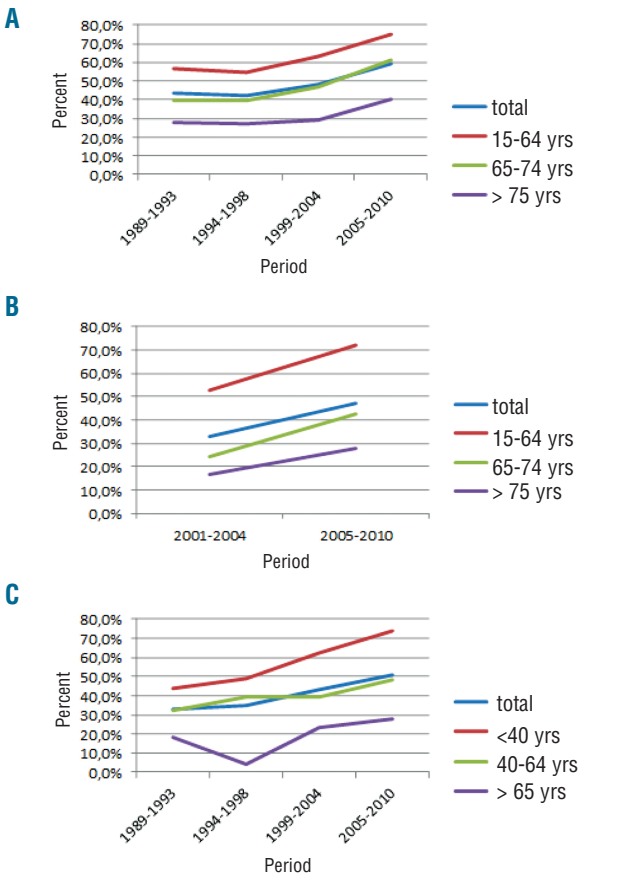

Figure 4. (A). Trends in 5-year relative survival for diffuse large B-cell lymphoma (DLBCL) according to age and period, in the Netherlands, 1989-2010. (B). Trends in 5-year relative survival for MCL according to age and period, in the Netherlands, 2001-2010. (C). Trends in 5-year relative survival for diffuse large B-cell lymphoma (DLBCL) according to age and period, in the Netherlands, 1989-2010.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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