THE TREATMENT OF ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA

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De behandeling van oudere patiënten met een agressief non-Hodgkin lymfoom

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The miracle isn't that I finished...
The miracle is that I had the courage to start.

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INTRODUCTION

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Contents Chapter 1

1.1. Non-Hodgkin's Lymphoma.

Non-Hodgkin's lymphomas (NHL) are neoplasms consisting of clonal proliferations of cells from the immune system. They encompass a heterogeneous group of diseases with a wide variety of histologic appearance, clinical behavior and prognosis. Several lymphoma classifications have been designed to make a distinction between disease categories that have a prognostic significance. The modern approach to the diagnosis of lymphoma includes a histologic diagnosis and analysis of the immunologic markers. The specific antigenic expression and immunophenotypic profile of the NHL cells are typical for the developmental stage of B- and T-cells, which are the normal counterparts of the NHL cell.

1.2. Classification systems.

The first classification system that was widely accepted was the Rappaport classification, introduced in 1956.(1) It divided the non-Hodgkin's lymphomas according to their architecture and cell morphology in nodular and diffuse growth patterns, and small ("lymphocytic") or large ("histiocytic") cells. Later it became clear that the large cells were in fact not histiocytic, but transformed lymphoid cells. The Rappaport classification has been revised, and more classifications were proposed, including those by Dorfman, Bennett (BNLI), Lukes-Collins, Lennert (Kiel) and WHO.(2-6) The Lukes-Collins and Kiel classifications incorporated phenotypic markers in their classification, or recognized B- and T-cell malignancies as separate entities. However, the use of different classification systems made a reliable comparison between clinical studies very difficult. Therefore the National Cancer Institute planned and sponsored a large study to assess the clinical applicability and reproducibility of the six major histo-pathologic classification systems of non-Hodgkin's lymphomas, based on clinical correlations. The result of this study, the Working Formulation (WF), was proposed as a comprehensive translation among the various systems. It recognized ten subtypes of non-Hodgkin's lymphoma, subdivided into three major prognostic groups, based on survival: low grade, intermediate grade and high grade.(7) The Working Formulation has been widely used as a classification system itself, although it did not incorporate modern diagnostic tools. The majority of clinical lymphoma studies refer to the WF subdivision into the three prognostic groups:

1) The low-grade lymphomas have a median survival of 5.1-7.2 years, and a 5-year survival of 50-70%. In the low-grade lymphoma group the small lymphocytic subtype consistent with CLL and "plasmacytoid" NHL (SL), the follicular NHL with predominantly small cleaved cells (FSL), and the follicular NHL with small cleaved and large cells (FM) were included.

2) The intermediate grade lymphomas have a median survival of 1.5-3.4 years and a 5-year survival of 33-45%. This group consists of the follicular predominantly large cell lymphoma (FL), the diffuse small-cleaved cell malignant lymphoma (DSC), the diffuse mixed small and large cell

lymphoma (DM) and the diffuse large cell lymphoma (DL).
3) The high-grade lymphomas have a median survival of 0.7-2.0 years, and a 5-year survival of 23-32%. This group comprises the large cell immunoblastic NHL (IBL), the lymphoblastic NHL (LBL) and the small noncleaved cell NHL (SNC).(7)
New and more immunologic, cytogenetic and molecular data prompted the need for a revision or even a new lymphoma classification system. It had been shown that specific genetic lesions may discern disease entities with a unique pathogenesis and clinical behavior. A new classification system was proposed. The "Revised European-American Classification of Lymphoid Neoplasms" (REAL) listed the currently well-defined disease entities. It described the histologic, immunologic and genetic features, and it mentioned the probable equivalents in the Rappaport, Kiel and Lukes-Collins classifications and the Working Formulation category. The clinical presentation and the course of the disease entities were shortly given, and the putative normal counterpart of each tumor was listed. This lymphoma classification also included Hodgkin's disease and lymphoid leukemias.(8) The lymphoma classification as proposed in the REAL has been slightly modified in the new WHO classification of leukemias and lymphomas that has recently been developed.(9) The WHO classification is the current classification standard of hematologic malignancies. However, many clinical studies have been based on the WF classification, and the older terminology has not yet disappeared. The intermediate and high-grade lymphomas will be described in brief in the next paragraph.

1.2.1. Intermediate-grade Non-Hodgkin's Lymphomas (WF terminology).

In the classical Working Formulation the intermediate-grade non-Hodgkin's lymphomas comprised of 4 different subgroups: follicular predominantly large cell, diffuse small-cleaved cell, diffuse mixed small and large cell and diffuse large cell lymphoma.

Follicular large cell lymphoma represented approximately 3% of NHL. The median age at presentation was 52-54 year.(10, 11) The division between follicular mixed (low-grade) and follicular large cell (intermediate-grade) NHL was difficult, since both have a follicular growth pattern, although in the follicular large cell NHL the large cells predominate. The REAL classification proposed the name follicle center cell lymphoma. It was separated into grade I, grade II, or grade III follicle center cell lymphoma, depending on the proportion of large cells.
The WHO classification recognizes follicular lymphoma as a well-defined entity, with at least a partially follicular pattern. It is graded according to the proportion of centroblasts. To achieve a more reproducible grading, the system of counting the absolute number of centroblasts is recommended.(12) The result is a 3-grade system, with follicular grade 3 having > 15 centroblasts

per high power field. If centrocytes are still present grade 3a can be used, in the case of sheets of centroblasts grade 3b is proposed. This subdivision seems to have a biologic and possible clinical importance.(13, 14) The entity follicular large cell lymphoma in the WF was as an intermediate grade lymphoma. In several studies therapy with a doxorubicin and cyclophosphamide containing regimen resulted in a much higher response rate and survival than other regimens designed for low-grade NHL, with the same response and 5-year overall survival as diffuse large B-cell lymphoma.(10, 11) So, it seemed reasonable to treat the follicular large cell lymphomas with an anthracycline and cyclophosphamide-containing regimen such as CHOP. The outcome of FL grade 3a and FL grade 3b was not significantly different with an anthracycline-containing regimen.(15) However, the need for anthracycline as front-line therapy of FL grade 3 is not supported by all groups.(16, 17)

Diffuse small-cleaved cell lymphoma (DSC) was the second group of intermediate grade lymphomas in the WF. It represented approximately 7% of all NHL and comprised most of the mantle cell lymphomas, but also part of the marginal zone lymphomas and the peripheral T-cell lymphomas.
The mantle cell lymphoma is nowadays recognized as a well-defined type of NHL. Generalized lymphadenopathy and frequent extranodal involvement characterize its clinical course. The presence of CD5 in the absence of CD23 is the typical phenotypic hallmark. The typical cytogenetic abnormality is t(11;14)(q13;q32), which results in dysregulation of cyclin D1. The median age at presentation is 68 years.(18) The prognosis is poor, with a median survival of 3 years. Mantle cell lymphoma is usually treated with cyclophosphamide, doxorubicin, vincristin and prednisone (CHOP). The overall survival after 10 years is 8%.(19) The duration of response and progression-free survival are significantly lower as compared to other intermediate or high-grade NHL. It is now generally accepted that mantle cell lymphoma has the worst characteristics of both low-grade and high-grade lymphomas, i.e. it is not curable and has an aggressive course.(20) Rituximab, a chimeric anti-CD20 monoclonal antibody, is an active compound against mantle cell lymphoma.(21) A regimen also incorporating high dose cytarabine followed by autologous stem cell transplantation may offer the best chances of long remission and possibly cure.(22)

Diffuse mixed small and large cell lymphoma represented approximately 7% of the lymphomas in the WF. Nowadays most of these lymphomas would be classified as T-cell rich B-cell lymphoma.

The largest subgroup of NHL is the diffuse large cell lymphoma. The subclassification in the Working Formulation between diffuse large cell NHL, immunoblastic NHL, and diffuse mixed small and large cell lymphoma was notoriously difficult, and complete agreement between different pathologists was rarely found.
In the WHO-classification most of these lymphomas are included in the single category diffuse large

B-cell lymphoma. A further subdivision in several morphologic variants is optional: centroblastic, immunoblastic (> 90% immunoblasts), T-cell/histiocyte rich (majority non-neoplastic T-cells, < 10% large neoplastic cells) and anaplastic (not to be confused with anaplastic large cell lymphoma, CD30 positive). It is very likely that the large heterogeneous group of diffuse large B-cell lymphomas will be subdivided in the future. These lymphomas have their origin in germinal center or post germinal center B-cells. This discrimination probably has prognostic significance.(23, 24)

The diffuse large B-cell lymphoma has a median age at presentation of 64 years. It is the most frequently diagnosed lymphoma, with 31% of cases.(25) The standard treatment is CHOP-chemotherapy, resulting in a 3-year overall survival of 52%, and a 3-year disease-free survival of 44%. Second and third generation regimens have not consistently shown any improvement of outcome.(26) More successful in improving the results of treatment of DLBCL was the addition of the anti-CD20 monoclonal rituximab to CHOP. This was demonstrated in a study which included only elderly patients.(27) More recently it has been demonstrated to be effective in younger good-risk patients too.(28) A similar improvement of outcome as with the addition of rituximab to CHOP has been observed by dose intensification of the CHOP-regimen, by giving it every 2 weeks. This also was demonstrated in elderly patients.(29) In these recent studies the follow-up is relatively short. However, late relapses are a rare event in these lymphomas.

1.2.2. High-grade Non-Hodgkin's Lymphoma.

Large cell immunoblastic lymphoma is considered a high-grade NHL in the WF. It comprised 8% of the lymphomas in the original report. In the WHO-classification it is included in the category of diffuse large B-cell NHL.

Lymphoblastic lymphoma is the non-leukemic presentation of acute B- or T-cell lymphoblastic leukemia. When untreated, it usually develops into acute leukemia. The disease is potentially curable with aggressive treatment. Precursor T lymphoblastic lymphoma is most common in young adults. Precursor B lymphoblastic lymphoma is relatively uncommon, less than 20% of lymphoblastic lymphomas.(30)

Many cases of small non-cleaved cell lymphoma in the WF would nowadays be classified as Burkitt lymphoma. Burkitt lymphoma typically has a t(8;14), t(2;8) or t(8;22) chromosomal abnormality, and usually presents with large extranodal tumors.(31) Three clinical variants are recognized. Endemic Burkitt lymphoma is most frequent in African children. Sporadic Burkitt lymphoma has no characteristic geographical distribution, and occurs mainly in children and young adults. Immunodeficiency associated Burkitt lymphoma is strongly associated with the human immunodeficiency virus (HIV) infection. Usually the tumor cells contain the Epstein-Barr virus (EBV) genome. The disease is potentially curable with intensive chemotherapy treatment, including central nervous system prophylaxis. After having obtained a complete remission, relapses after one year are rare.

1.2.3. Clinical significance of the WHO classification.

Shortly after its publication the implications of the REAL/WHO classification of non-Hodgkin lymphomas have been evaluated. It became clear that new entities were now clearly defined, and that indeed immunophenotyping was very useful in the diagnostic process of some lymphoma types.(25) The better discrimination of lymphoma types probably will result in more specific therapy and thus a better prognosis.

An important question is whether the distribution of pathologic entities is different in elderly patients, and if so, whether this may account for the relatively poor outcome of therapy at higher age. Our knowledge about the distribution of various pathologic entities in different age groups is limited to a few studies. The NHL of low-grade malignancy comprised 30% of the total group of NHL in the elderly, and 25-30% was high-grade.(32) The distribution among the several subgroups of the WF showed no difference between patients above and below 60 or 65 years of age.(33-35)
Pathologists and clinicians of The Non-Hodgkin's Lymphoma Classification Project studied the effect of age on the frequency, clinical characteristics and outcome of the different lymphoma entities as described in the REAL-classification.(36) Diffuse large B-cell lymphoma was the most frequently diagnosed entity. 21% of the cases were diagnosed in patients 60-69 year old, 32% in patients 70 year or older. The distribution of patients in the four groups of the age-adjusted prognostic index (AAPI) was quite homogeneous. The survival of patients with DLBCL decreased with increasing age. This study clearly demonstrated that age is an important factor for outcome, but also that histologic classification and clinical characteristics (such as the AAPI score) are necessary to determine the prognosis.

2. Molecular pathogenesis.

The molecular pathogenesis of non-Hodgkin's lymphomas (NHL) is gradually being elucidated. In some lymphoma types a specific genetic abnormality is an important defining criterion. A nonrandom chromosomal rearrangement may play a key-role in the process of malignant transformation. In such cases, usually one of the proto-oncogenes is juxtaposed to regulatory elements of genes expressed normally in the cells, most frequently immunoglobulin genes. This results in the activation of oncogenes. The resulting protein product may affect many cellular functions including proliferation and differentiation. An alteration in genes may be microscopically visible as a change in chromosomal structure, but in most cases it is only detectable by molecular analysis.

Certain subtypes of lymphomas are associated with specific cytogenetic abnormalities, such as the well-known translocation t(14;18) in follicular lymphomas.
In lymphomas of intermediate or high-grade malignancy specific chromosomal translocations are rare.

2.1. Burkitt lymphoma.

The translocation t(8;14) is found in 90% of Burkitt lymphomas. Less frequently the t(2;8) and t(8;22) translocations which are present in 5% of Burkitt lymphomas are observed. In these translocations the *myc* gene, located on chromosome 8, is juxtaposed to the DNA-sequences of the immunoglobulin genes resulting in a disrupted regulation of *myc*. This translocation is also present in 5-7% of the large B-cell lymphomas.(37, 38) Diffuse large cell lymphomas in the gastro-intestinal tract have the highest incidence, 28%.(39)

2.2. Mantle cell lymphoma.

Another clinico-pathologic entity with a specific translocation is mantle cell lymphoma. In the majority of cases a translocation t(11;14)(q13;q32) is observed. Juxtaposition of the *bcl*-1 locus to the immunoglobulin gene on chromosome 14 results in overexpression of cyclin D1. This protein belongs to the family of cyclins that is involved in the regulation of the cell cycle. mRNA expression of cyclin D1 has been found in cases of mantle cell lymphoma which lack detectable *bcl*-1 rearrangements, which suggests that additional (minor) breakpoint sites are involved in the translocation of chromosome 11q13. In other histological entities within NHL this translocation is rarely observed.

2.3. Diffuse large B-cell lymphoma.

2.3.1 bcl-2.

The most frequently diagnosed lymphoma type is diffuse large cell lymphoma. In this very heterogeneous group of lymphomas, cytogenetic analysis may sometimes reveal a translocation t(14;18).(40) If present, the t(14;18) translocation gives rise to the activation of the *bcl*-2 gene, like in low-grade lymphomas, resulting in impaired apoptosis. The extent to which *bcl*-2

is activated is still not clear. Analysis of *bcl-2* protein expression by immunohistochemistry and analysis of major breakpoint region (MBR) rearrangements by polymerase chain reaction (PCR) assay produce conflicting results.(41, 42) With immunostaining a high *bcl-2* expression is found in 45-56% of the large cell lymphomas, while *bcl-2*-MBR gene rearrangement is found less frequently (10-20%).(41-46) *Bcl-2* expression has a prognostic relevance in diffuse large cell lymphoma. A higher relapse rate and a shorter survival and disease-free survival are observed in *bcl-2* positive cases.(37, 41, 44, 45, 47) So far it appears that for long time survival *bcl-2* protein expression is a significant adverse prognostic factor, whereas *bcl-2* gene rearrangement status has no impact on outcome.(42)

2.3.2. p53.

Another gene that may play a role in development of neoplasia and/or response to treatment is p53. This gene is located on the short arm of chromosome 17. p53 is a tumor suppressor gene, which is involved in the transcription of other genes that repress cell proliferation. p53 induces the synthesis of the p21 protein, which inhibits cyclin-dependent kinase. As a result, cells in G1 phase of the cell cycle are arrested temporarily. Mutations of p53 have been described in many tumors, and may account for increased cell proliferation. Normally, p53 is rapidly degraded after synthesis, but mutated p53 proteins may accumulate in the cells. Mutations of p53 have been found in B-cell and T-cell lymphomas. p53 mutations appear to be associated with the presence of other poor prognostic markers, i.e. higher age, higher clinical stage and high serum lactate dehydrogenase (LDH). In diffuse large B-cell lymphomas the frequency of p53 positivity is 13-32%.(43, 45, 47) Some studies report an adverse impact of p53 expression on overall and disease free survival in large cell lymphomas.(43, 48-51) Other studies find no effect of p53 expression or mutation.(45, 47, 52) p53 mutations, rather than p53 expression, have a significant adverse effect on the CR-rate and overall survival in NHL.

2.3.3. bcl-6

Another translocation, which involves the breakpoint 3q27 results in deregulation of the bcl-6 gene. The bcl-6 gene encodes a member of the zinc finger family of proteins that regulate differentiation and development. The bcl-6 protein is expressed by B and T-cells in the germinal center. It is necessary for germinal center formation, as has been demonstrated with bcl-6 knockout mice. Approximately 40% of diffuse large cell lymphomas express a rearranged bcl-6 gene. Deregulated bcl-6 expression is associated with increased bcl-6 protein levels. The survival curve of patients with rearranged bcl-6 shows a plateau, suggesting a better prognosis in the case of a bcl-6 rearrangement.(53-55) A high level of bcl-6 mRNA correlated with a better prognosis.(56)

2.3.4. DNA microarray results.

Recently, the DNA microarray technique has been able to subdivide the large group of diffuse large B-cell lymphoma in two subgroups with a different gene expression profile.(23) These two subgroups, germinal center B-cell (GCB) and activated B-cell type (ABC), have a different outcome, the GCB type having a much more favorable prognosis. In a larger group of patients a third subgroup is recognized, the type 3 diffuse large B-cell lymphoma. A combination of 17 genes has been found to predict for overall survival after chemotherapy treatment, independent from the international prognostic index (IPI).(57) Germinal center B-like DLBCL can be discriminated from non germinal B-cell (non-GCB) DLBCL with immunohistochemistry. This method is simpler and more widely available than DNA microarray. Studies on the prognostic significance of the immunophenotyping profile show conflicting results.(47, 58) However, a study comparing data from DNA microarray with the results of tissue microarray describes that a panel of 3 immunostains might predict the non-germinal B type DLBCL correctly in 88%.(24) A study in previously untreated elderly patients with DLBCL applying the same 3 immunohistochemical stains (CD10, bcl-6 and MUM1) could not confirm the prognostic significance of the GCB and non-GCB type. A new prognostic immunophenotypic profile that discriminated good from poor prognosis was suggested: cannaboid receptor CB2 and CD40.(59)

Non-Hodgkin's lymphomas of intermediate or high-grade malignancy in elderly patients have a worse prognosis than in younger patients. There is no data suggesting that this is based on different genetic lesions. Unfortunately, the presence of specific molecular changes in different age groups in large clinical studies can not be determined with certainty since only a third of the patients were older than 60 years in most published studies. So far, no association between abnormal *bcl-2*, p53 or bcl-6 expression and age has been found. In a population based study of non-Hodgkin's lymphomas in the south western part of the Netherlands *bcl-2* or p53 overexpression had no prognostic significance for the elderly (> 65 years) patients.(60)

Molecular analysis has led to improvement in our understanding of the biology and the pathogenesis of various histologic subgroups of non-Hodgkin's lymphoma. Several of these genetic changes may also have prognostic significance, yet these new diagnostic tools are not ready for use in clinical practice due to technical complexity. Various techniques, i.e., microarray, cytogenetics, PCR, FISH and immunohistochemistry are now rapidly coming available and will have an impact on our understanding of the prognosis of the disease in individual patients. In the future these new techniques may become a part of the NHL classification systems and contribute to the design of risk adapted treatment.

3. Epidemiology and etiology.

The incidence of non-Hodgkin's lymphoma is increasing gradually but steadily. It has been questioned whether this is a real increase or possibly the result of better diagnostic techniques. Changes in diagnostic criteria can not explain the striking increase of lymphoma incidence.(61) Nowadays it is agreed upon that it is a real increase, and it is observed around the world.(62, 63) According to SEER data (Surveillance, Epidemiology, and End Results) of the National Cancer Institute the net increase of incidence rates is 3-4% per year.(64, 65) In contrast, the incidence rates of Hodgkin's disease have not changed. The rising incidence of NHL is seen in almost all of the cancer registries.

The incidence rates increase among all age groups although the increase is larger in the elderly. This is not only explained by a rise in life expectancy of the general population. The proportion of the elderly population is gradually increasing, but the increase is demonstrated per year-of-birth cohort.(66) Only since the 1980's a sharper increase can be found in younger men, below 54 years, which is probably related to the AIDS epidemic.(62, 65) Since the introduction of highly active anti-retroviral therapy (HAART) the incidence of the AIDS-related lymphoma between young males has decreased, but the rise in incidence of non-AIDS related lymphomas has continued so far.(67)

From the late 1940's to the late 1980's the age-adjusted incidence rates of NHL increased 150% among Caucasian men and women. The mortality rates increased 85-100%, with a plateau during the late 1960's through the late 1970's. The curves for white males, white females, nonwhite males and nonwhite females are parallel. The age-specific mortality increased in each age group from 55 years and older, with the rate of increase being larger in each successive age group. The mortality declined among young persons.(65)

There are considerable differences in incidence rates between sexes and races. White males have the highest incidence and mortality rates and non-white females the lowest risk. In the time period 1984-1988 the incidence rates (per 100.000 person-years) were 16.6 in white males, 11.2 in white females, 10.5 in black males and 6.9 in black females. Before the 1970's the mortality rates from NHL were 40% higher in urban counties as compared to rural areas. This difference has diminished gradually over time, while the mortality rates increased more rapidly in rural areas. The major different lymphoma subtypes have specific characteristics concerning incidence rate per sex, race, and geographical distribution.(68)

The incidence of extranodal lymphomas has increased proportionally more than nodal lymphomas. Most extranodal lymphomas present in the stomach, skin, and the central nervous system. The largest increases between 1974 and 1988 were noticed in the central nervous system and the eye.(68)

Epidemiologists consider time trends of disease incidence important for a better understanding of the relevant etiologic factors. HIV is not an oncogenic virus, but HIV-infection may result

in increasing rates of DLBCL or Burkitt lymphoma by impairment of cell mediated immunity. Another virus, human T-cell leukemia virus-1 (HTLV-1) a small retrovirus, is responsible for a small number of lymphomas. The virus is endemic in Japan and the Carribean. Carriers of the HTLV-1 have a cumulative risk of ATLL of 1-5%.(69) The prevalence of this virus in the western world is very low, and can not account for the rising incidence and mortality of NHL.

Epstein-Barr virus infections have also been associated with lymphomas, especially in patients who are treated with immunosuppressive drugs.(70) However, this is a ubiquitous virus, of which the prevalence has not changed. It therefore can not simply explain a change in incidence of NHL. Organ transplantation or the use of immunosuppressive drugs may enhance the risk of developing NHL, but this accounts for a very small group of patients.(71)

Autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome, but also asthma and allergies have a modest association with increased NHL risk.(72, 73) A chronic antigenic stimulation probably increases B-cell proliferation, which increases the risk of a random genetic mistake, particularly related to immunoglobulin gene rearrangements.(74) Moreover, T-cell function may be impaired, so interfering with the immune response to emerging malignant cells.

Another condition that supports the role of chronic antigenic stimulation and the risk of developing lymphoma is infection with Helicobacter pylori (Hp). It causes chronic gastritis, is necessary for peptic ulcer formation and is present in most cases of gastric MALT (mucosa- associated lymphoid tissue) lymphoma.(75) Hp eradication with antibiotic therapy cures the lymphoma, although monoclonal B-cells may still be present.(76)

Exposure to industrial solvents, herbicides and hair dyes has been proposed as an etiological factor. The percentage of patients with occupational contact with these possible risk factors is low. However, the non-occupational contact with these factors has certainly increased over the last forty years. No clear relation between lymphoma and tobacco use has been demonstrated, although a slight increase in the incidence of follicular lymphoma in women has been observed.(77, 78) A relation between the rising lymphoma incidence and alcohol use also seems very unlikely. Alcohol use in some studies was inversely correlated with lymphoma risk.(79, 80) Changes in diet may also contribute to the rising lymphoma incidence. The increase in incidence by year-of-birth cohort and the relative greater increase in older individuals suggest that exposure to one or more environmental factors play a role. A changing immune response to antigens may also be important.

It can be concluded that the incidence of NHL is rising, but that a single good explanation is lacking.

4. Clinical manifestations.

A large proportion of patients with non-Hodgkin's lymphoma or Hodgkin's disease present with localized or generalized lymphadenopathy. General symptoms may be present, i.e., weight loss, fever or night sweats. These symptoms are called "B-symptoms". Fatigue is also a common complaint.

If the lymphadenopathy is limited to one site a metastatic carcinoma must be excluded. Infections usually result in painful nodes, but rapidly expanding malignant nodes may also be tender.

Sometimes splenomegaly may be the presenting symptom of NHL. Anemia or pancytopenia may be present as a result from bone marrow infiltration by lymphoma cells. Immunologic events, such as Coombs positive hemolytic anemia, may be the presenting symptom. Such hemolysis may be severe and life threatening, and is not related to the tumor bulk.

Extranodal localizations of NHL are relatively frequently observed in elderly patients. Lymphomas may arise in the stomach, the skin, and the central nervous system, but also the thyroid gland, liver, intestines, adrenal gland, kidney, testes and eye may be primarily involved. After a detailed history and physical examination, a complete blood count, peripheral blood smear and erythrocyte sedimentation rate should be done. Lactate dehydrogenase level (LDH) may be raised in case of hemolytic anemia, but if no hemolysis is present it is a poor prognostic factor.

A lymph node biopsy or a tissue biopsy in case of extranodal lymphoma is required to establish a definitive diagnosis of NHL in patients with persistently enlarged lymph nodes. It is necessary to perform a cytological aspiration upon suspicion of certain cases of localized NHL. However, in order to classify NHL properly a histologic examination is needed. Fresh specimens can be used for frozen histology and for immunophenotyping, molecular analysis and other specialized procedures that are in selected cases helpful for adequate diagnosis.

In elderly patients a proper diagnosis is as important as in younger ones. Once the malignancy grade, stage of disease and risk factors are known, a definitive estimation of the patient's prognosis can be given. The discussion about a potential curative therapy, but also about palliative measures completely depends on a good evaluation of these prognostic factors.

5. Staging

When non-Hodgkin's lymphoma has been diagnosed the next important step is staging. The classical staging method according to the Ann Arbor classification was published in 1971, originally to stage Hodgkin's disease (table 1).(81) This clinical staging procedure is based on the

medical history, physical examination, radiographic examination, laboratory results and the results of biopsies from suspected nodes or organs. B-symptoms are defined as an unexplained weight loss of more than 10% of the body weight during the past six months, unexplained fever above 38 °C, or recurrent drenching night sweats during the previous month. It should be emphasized that the staging classification only applies at the time of disease presentation.

Since the introduction of new techniques to evaluate sites of disease involvement, e.g. computed tomography (CT scanning) or magnetic resonance imaging (MRI) a staging laparotomy is no longer needed. CT evaluation of the entire thorax, abdomen and pelvis using intravenous contrast with images at 1 cm intervals is mandatory. Lymph nodes of more than 1.5 cm cross sectional diameter are unequivocally considered disease involvement.(82) MRI might be useful for documentation and follow-up of certain extranodal lymphoma localizations.

Spleen involvement is diagnosed by unequivocal palpable splenomegaly, or by equivocal splenomegaly with radiological confirmation of either enlargement or multiple focal defects that are neither cystic nor vascular. Radiological enlargement alone is inadequate.

Liver enlargement may be diagnosed by multiple focal defects which are neither cystic nor vascular noted with at least two imaging techniques. Clinical enlargement alone with or without abnormalities of liver function tests is not adequate.

A node or nodal mass 10 cm or greater is designed “bulky”. The bulk of palpable nodes is defined as the largest dimension (cm) of the single largest lymph node or conglomerate node mass in each region of involvement. A mediastinal mass is defined as “bulky” when the maximal width on a posteroanterior chest radiograph is equal or greater than one-third of the internal transverse diameter of the thorax at the level of T5/6.

The mediastinum includes several nodal subgroups: (a) prevascular, aortopulmonary; (b) paratracheal, pretracheal, subcarinal; (c) posterior mediastinal. Hilar (bronchopulmonary) nodes are considered outside the mediastinum. If both sides are involved, at least stage II is present.

Table 1. **Ann Arbor staging classification.**

Stage I.	Involvement of a single lymph node region or single extralymphatic organ or site (IE).
Stage II.	Involvement of two or more lymph node regions on the same side of the diaphragm, or localized involvement of extralymphatic organ or site and of 1 or more lymph node regions on the same side of the diaphragm.
Stage III.	Involvement of lymph node regions on both sides of the diaphragm, which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE).
Stage IV.	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

The lymphatic structures comprise the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches. Liver involvement is always considered to be diffuse, and therefore stage IV. B-symptoms: unexplained weight loss of more than 10% of the body weight during the past six months, or unexplained fever above 38 °C, or recurrent drenching night sweats during the previous month.

It is important to realize this classical staging system has been originally designed for Hodgkin's disease. However, it is also widely used for non-Hodgkin's lymphoma. In Hodgkin's disease the four different stages have a significant impact on the survival and disease free survival. In NHL the pattern of disease dissemination is different, and here a relation with prognosis is less evident, even if low-grade and high-grade lymphomas are analyzed separately. The distribution of histologic subtypes of NHL over the various stages is not even.(83) For example, the follicular lymphomas have a high percentage of bone marrow involvement, and stage I and II are a minority, while more aggressive lymphomas frequently present with stage I-II disease. However, the Ann Arbor classification is an important clinical tool to designate the patients in various risk categories. The result of the staging procedure is one of the determinants of the "International Prognostic Index".(84)

In elderly patients incomplete staging is quite frequent. In a Dutch population based study 30% of the patients 70 years or older were staged incompletely. The bone marrow biopsy contributed to the incomplete staging in 74%.(85)

The response to treatment should be documented, based on clinical evaluation and imaging investigations of the same lesions that were abnormal at presentation and tissue biopsies should be taken when appropriate. A complete remission implies the patient has no evidence of disease. Partial remission is defined as reduction by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions. There should be a resolution of all B-symptoms. Progressive disease is defined as a 25% or more increase in the size of at least one measurable lesion, or the appearance of a new lesion, or recurrence of B-symptoms.(86)

In the near future, ^{18}FDG-PET scintigraphy will probably be used in the staging and response evaluation of malignant lymphoma. It has already been shown that FDG-PET detects more lymphoma lesions than conventional staging, and results in changes of treatment plan in up to 18% of cases.(87, 88) The results of PET scintigraphy might be important for prognosis, although the exact timing of the scintigraphy and clinical consequences are not clear at the moment.(89, 90)

6. Treatment

Over the past 30 years the treatment of non-Hodgkin's lymphoma has gradually improved. Initially it was recognized that single agent chemotherapy induced tumor regressions and occasionally a complete remission. However, the disease-free intervals were usually short.

6.1. CHOP.

In 1971 the first results of combination chemotherapy in NHL, i.e., cyclophosphamide, vincristine and prednisone (COP) were reported.(91) Two years later the addition of adriamycin to this regimen (CHOP) led to an impressive improvement of the results, in particular because a larger contingent of patients showed a complete or partial response.(92) DeVita published encouraging results of nitrogen mustard, vincristine, procarbazine and prednisone (MOPP) and C-MOPP (MOPP plus cyclophosphamide) in the treatment of diffuse histiocytic lymphomas. 10 of 27 patients were in ongoing complete remission for over 2 years following treatment. For the first time NHL was recognized as a potentially curable disease.(93) The Southwest Oncology Group (SWOG) compared the classical CHOP-scheme (table 2) with HOP (adriamycin, vincristine and prednisone), and it was found that CHOP was superior, with a complete remission rate of 71% in evaluable patients.(94)

Table 2. **The CHOP regimen.**

Agent	Dose
Cyclophosphamide i.v.	750 mg/m^2 day 1
Doxorubicin i.v.	50 mg/m^2 day 1
Vincristine i.v.	1,4 mg/m^2 , day 1 (maximum dose 2 mg)
Prednisone orally	100 mg, day 1-5 (95)

To repeat on day 22.

6.2. Second and third generation regimens.

Many multi-drug chemotherapy regimens have been published since (table 3). These regimens were largely based on the hypothesis of Goldie and Coldman, which implies that early exposure of tumor cells to multiple non-cross-resistant drugs minimizes the risk of development of drug-resistant cells.(96) Phase II studies with these second and third line regimens suggested that the complete remission and overall survival rates were superior to CHOP. Some randomized studies have been performed comparing CHOP or a CHOP-like regimen with other CHOP-like regimens.(97-107) No significant improvement of survival has been demonstrated with any of the regimens, while toxicity of some of them was considerably higher than with CHOP. Between 1986 and 1991 SWOG and the Eastern Cooperative Oncology Group (ECOG) have performed a large prospective multicenter randomized phase III trial, to compare CHOP, m-BACOD, ProMACE-CytaBOM and MACOP-B. The conclusion is that CHOP is the best available treatment for patients with advanced stage intermediate-grade or high-grade non-Hodgkin's lymphoma.(26)
Replacement of agents in the CHOP regimen to reduce certain toxicities has also been studied. So has vincristine been replaced by teniposide. This resulted in less neuropathy, but an increase in myelosuppression. No difference in outcome was observed.(108)
The cardiotoxic doxorubicin has been replaced by the less cardiotoxic idarubicin. This resulted in an equivalent outcome of treatment with respect to CR-rate and survival. Patient numbers were too small to find a significant difference in clinical cardiotoxicity.(109)
Interferon has some efficacy in the treatment of follicular lymphoma.(110, 111) Addition of interferon to CHOP and 1 year maintenance therapy has also been studied in large cell lymphoma. It did not improve the outcome of treatment.(112)

Nowadays CHOP is accepted as the standard treatment with which new promising treatment regimens should be compared in a prospective randomized fashion.
Intensification with high dose chemotherapy and autologous stem cell transplantation has not been shown to improve outcome compared to standard dose chemotherapy.(113-116) However, a better disease free survival and overall survival has been observed with autologous stem cell transplantation compared to standard chemotherapy as intensification after attaining a CR in a subgroup analysis of the higher risk patients in the LNH-87-2 protocol.(117)

Table 3. **Second and third generation chemotherapy regimens.**

Regimen	Agents	CR-rate	Survival	References
COP-BLAM	Cyclophosphamide Vincristine Prednisone Bleomycin Doxorubicine Procarbazine	73%		Laurence et al, 1982.(118)
ProMACE-MOPP	Prednisone Methotrexate Doxorubicin Cyclophosphamide Etoposide Mechlorethamine Vincristine Procarbazine	74%	65% at 4 years	Fisher et al, 1983.(119)
M-BACOD	Bleomycin Doxorubicin Cyclophosphamide Vincristine Dexamethason Methotrexate	72%	80% at 5 years	Skarin et al, 1983.(120)
MACOP-B	Methotrexate Doxorubicin Cyclophosphamide Vincristine Bleomycin Prednisone	84%	76% at 2 years	Klimo et al, 1985.(121)
COMLA	Cyclophosphamide Vincristine Methotrexate Leucovorin Cytarabine	80%	66% at 2 years	Baer et al, 1986.(122)

Table 3. **Second and third generation chemotherapy regimens,** continued.

Regimen	Agents	CR-rate	Survival	References
LNH-84 (ACVBP + consolidation)	Doxorubicin Cyclophosphamide Vindesine Bleomycin Prednisolone Methotrexate Ifosfamide Etoposide Asparaginase Cytarabine	75%	62% at 2 years	Coiffier et al, 1989.(123)
ProMACE-CytaBOM	Cyclophosphamide Doxorubicin Vincristine Methotrexate Bleomycin Cytarabine Etoposide	86%	69% at 5 years	Longo et al, 1991.(124)
PACEBOM	Prednisone Doxorubicin Cyclophosphamide Etoposide Bleommycin Vincristine Methotrexate	57%	47% at 3 years	Sweetenham et al, 1991.(125)

6.3. Treatment of elderly patients.

While the second- and third-generation chemotherapy regimens were developed in the hope that dose-intensification through incorporation of more drugs would increase response and survival, it was recognized that older patients with NHL tolerated CHOP or CHOP-like chemotherapy less well. In many trials older patients were underrepresented or not included at all.

Armitage published a first analysis of the specific problems that were encountered with patients more than 70 years old who were afflicted with NHL. He observed that 25% of those patients died during the first or second treatment cycle. In the surviving patients the response rate was comparable to younger NHL patients.(126) A retrospective analysis of two large SWOG clinical trials, which had included elderly patients, demonstrated that the complete response rate and survival declined with higher age.(127) This could be explained by the then ruling custom to reduce the dose of cytostatic agents by 50% in patients above 65. Not surprisingly, dose reduction is associated with less toxicity and consequently, early treatment related deaths are not different

between various age groups. In several clinical trials age has been found to be the most significant adverse prognostic factor. In a French study the relapse rate in elderly patients was higher.(128) In a study by the Nebraska Lymphoma Study Group patients older than 70 years with diffuse aggressive NHL received a one third dose-reduction. The complete remission rates and the relapse rate were identical for the elderly and patients below 70. There was, however, a significant better 5-year survival in the age group below 60 years (62 versus 34%). This could not be attributed to a difference of recurrent lymphoma, treatment related toxicity or treatment related toxic death rate (7% in all age groups). However, in elderly patients significantly more unrelated deaths occurred, which were mainly related to cardiovascular causes and other malignancies.(129) From these studies it can be concluded that there is general agreement about the adverse effect of age on treatment outcome due to different causes (table 4).

Table 4. **Potential causes of treatment failure in elderly patients with NHL**

- increased treatment related toxicity
- ineffective dose or inadvertent dose reduction
- non-disease related mortality or morbidity
- lack of compliance to treatment protocols
- altered pharmacokinetics/dynamics
- predominance of histologic entities with poor prognosis

6.3.1. Treatment regimens for elderly patients.

Because elderly patients tolerate chemotherapy less well, treatment schedules have been developed that are specifically designed for this age group. Most regimens are based on eliminating a drug or reducing effective agents from standard multi-drug chemotherapy regimens in order to reduce toxicity.
The “conservative” approach is based on palliative treatment with single agents, local radiotherapy or attenuated CVP.(32, 130, 131) However, the response, if any, is usually of short duration, as is the overall survival. It is therefore questionable if “mild” cytotoxic therapy should be preferred as a palliative treatment over symptomatic therapy.
More recently, and based on these results, several treatment schedules have been designed that are based on combination chemotherapy. These regimens are composed of agents that have fewer side effects but aim at a minimum loss of efficacy. Examples of such attempts are the V(M)P schedules based on oral administration of etoposide and prednimustine, to which later mitoxantrone was added to improve outcome.(132-134)

Table 5. **Regimens specifically designed for elderly patients with NHL, nonrandomized studies.**

Regimen	Agents	Results CR-rate	Toxicity	References
CNOP	Cyclophosphamide Mitoxantrone Vincristine Prednisone	60%	7% grade 4 neutropenia	Sonneveld et al, 1990.(135)
CMPP	Chlorambucil Mitoxantrone Procarbazine Prednisolone	32%	18% grade 4 neutropenia	Watkin et al, 1990.(136)
IE	Ifosfamide Etoposide	47%	18% grade 4 hematologic	Tigaud et al, 1991.(137)
LD-ACOP-B	Doxorubicin Cyclophosphamide Vincristine Bleomycin Prednisone	65%	24% ≥ grade 3 neutropenia	O'Reilly et al, 1991.(138)
VABE	Etoposide Doxorubicin Vincristine Bleomycin Prednisone	63%	91% ≥ grade 3 neutropenia	O'Reilly et al, 1991.(138)
BECALM	Bleomycin Etoposide Cyclophosphamide Doxorubicin Methotrexate Leucovorin Prednisone	42%	58% ≥ grade 3 neutropenia	McMaster et al, 1991.(139)
VMP	Etoposide Mitoxantrone Prednimustine	46%	32% of cycles ≥ grade 3 hematologic	Tirelli et al, 1992.(134)
VNCOP-B	Etoposide Mitoxantrone Cyclophosphamide Vincristine Prednisone Bleomycin	76%	41% dose delay because of neutropenia	Zinzani et al, 1993.(140)
COPP	Cyclophosphamide Vincristine Procarbazine Prednisone	37%	28% neutropenic infections	Liang et al, 1993.(33)

Table 5. **Regimens specifically designed for elderly patients with NHL, nonrandomized studies,** continued.

Regimen	Agents	Results CR-rate	Toxicity	References
P/DOCE	Epirubicin or Doxorubicin Vincristine Cyclophosphamide Etoposide Prednisone	62%	20% neutropenic fever 69% grade 3 neutropenia 18% mucositis grade 3-4 (DOCE) 7% mucositis grade 3-4 (POCE)	O'Reilly et al, 1993.(141)
P-VABEC	Doxorubicin Etoposide Cyclophosphamide Vincristine	75%	No grade 4 neutropenia 37% mucositis grade 2-4 37% neurotoxicity gr. 2-4 15% cardiac toxicity grade 2-4	Martelli et al, 1993.(142)
	Bleomycin Prednisone	75%	14% grade 4 neutropenia 9% grade 2 mucositis	Caracciolo et al, 1994.(143)
P-VEBEC	Epirubicin Cyclophosphamide Etoposide Vinblastine Bleomycin Prednisone	66%	42% G-CSF support 57% grade 4 neutropenia if no G-CSF support 6% ≥ grade 3 infections	Bertini et al, 1994.(144)
MCOP	Mitoxantrone Cyclophosphamide Vincristine Prednisolone	63%	9% ≥ grade 3 neutropenia	Bessell et al, 1994.(145)
PEN	Prednisone Etoposide Mitoxantrone	42%		Goss et al, 1995.(146)
	Etoposide Cytarabine Methylprednisolone Methotrexate	40%	56% dose reduction due to myelotoxicity	Novitzky et al, 1995.(147)
THP-COPBLM	Pirarubicin Cyclophosphamide Vincristine Prednisone Bleomycin Procarbazine	73%	Including G-CSF support 31% ≥ grade 3 leucopenia	Niitsu et al, 1997.(148)

Other regimens are based on the assumption that anthracyclins, such as doxorubicin should be replaced by less toxic agents in order to diminish the gastrointestinal and cardiac toxicity, or modified well-known regimens to reduce toxicity (table 5). So far, the majority of clinical studies of NHL treatment in the elderly patient were performed as phase II trials, in order to find a regimen with an acceptable toxicity without losing effectiveness. Although such regimens might be well tolerated and the results were promising compared to the literature data, it was impossible to draw conclusions regarding the effectiveness in the general population. Interpretation of the results of these trials is hampered by several factors. Some trials reported response rates of a heterogeneous group of patients, i.e., with "low-grade" and "intermediate-/or high-grade" histology. Others reported the results of a mixed group of previously treated and untreated patients.

It was often suggested that elderly patients can not tolerate standard chemotherapy, and that this patient group needed specifically designed schedules. However, standard chemotherapy regimens may be suitable for at least part of the elderly patients. In a study in which 30% of patients were older than 65 years the overall 3 year survival of the patients above 65 years was identical to the survival of the younger patients (58 versus 65%) with full-dose chemotherapy (CHOP or m-BACOD). This study suggested that the majority of elderly patients can be treated with standard dose adriamycin containing regimens.(34)
The national high priority lymphoma study in the USA, that compared four chemotherapeutic regimens, concluded that CHOP remains the best available treatment for patients with aggressive non-Hodgkin's lymphoma.(26) The projected 5-year survival rates were similar in patients above and below 60 years. The MACOP-B arm showed a significant higher percentage of fatal toxicities in the elderly.(149) Patients older than 60 treated with CHOP, m-BACOD or ProMACE-CytaBOM had similar survival rates as their younger counterparts.

6.3.2. Treatment of elderly patients, randomized studies.

Few randomized studies specifically designed for elderly patients have been published. The Hamilton Regional Lymphoma Group compared standard dose CHOP with a weekly administration of one third of the chemotherapy dose, to determine whether elderly patients tolerated this better. The average received dose-intensity was identical. They could demonstrate no difference in the toxicity profile and 2-year survival. So, attenuation of standard CHOP did not lead to better treatment results.(150)
In a prospective randomized multicenter phase III clinical trial the effectiveness and tolerability of CHOP was compared to the same regimen except replacement of doxorubicin by the less cardiotoxic agent mitoxantrone (CNOP). Both regimens were administered every 4 weeks. The median age in this study was 71 years. The toxicity in both arms was comparable, except for alopecia and nausea, which were more frequent with CHOP. The CR-rate of CHOP was significantly better than the CR-rate of CNOP, 49% versus 31%, and the overall survival for patients treated with CHOP was significantly better, 42% versus 26% at 3 years. The survival in different age groups was not different. Considering the absence of a difference in toxicity and a better response rate and survival, CHOP was recommended for the treatment of high-risk NHL in elderly patients.(151)

Another multicenter randomized study also compared adriamycine with mitoxantrone. PACEBOM, a third generation CHOP-like regimen, had proved to be comparable with CHOP.(102) To diminish the high rate of mucositis the methotrexate had been omitted, resulting in PACEBO. Adriamycin was replaced by mitoxantrone to reduce the cardiotoxicity of the regimen. Patients treated with PMitCEBO had a better response rate and significant better overall survival. The toxicity of both regimens was identical.(152) It is unclear why the mitoxantrone containing regimen in this study was better than the adriamycin containing regimen. A randomized study comparing CHOP with CNOP as initial therapy in patients 16 years or older reported no difference in survival. (153)
The GELA (Groupe d'Etude des Lymphomes de l'Adulte) organized a large multicenter trial for patients 70 years or older with an intermediate- or high-grade NHL to study whether an anthracyclines analog could be omitted from combination chemotherapy. They compared cyclophosphamide, teniposide and prednisolone (CVP) with CVP plus the anthracycline analog pirarubicin (THP-Adriamycin) (CTVP). The median age was 75 years (range 70-90). Neutropenia was more frequent in the CTVP arm, but no significant difference in frequency and severity of infections was observed. The CR-rate was significantly higher in the CTVP arm (47% vs 32%). The 5-year survival rate was 27% and 19% respectively. Survival was not related to age. The anthracycline-containing regimen resulted in a better progression-free survival and 5-year survival.(154)
The EORTC (European Organization for Research and Treatment of Cancer) lymphoma group compared etoposide, mitoxantrone and prednimustine (VMP), with standard CHOP in patients 70 years or older with intermediate- or high-grade NHL. Patients with a poor performance status

(PS 2 or 3) started with a reduced dosage. The scheduled six cycles of chemotherapy could be administered to 56% of the patients. No significant difference in the occurrence of hematologic toxicity was found. Infection was reported in 36% of patients, in both arms in identical frequency. No difference in clinical cardiotoxicity was reported. Significant differences in toxicity were gastrointestinal, neurologic, and alopecia, all being more frequent in the CHOP arm. The response to treatment was significantly better in the CHOP arm, i.e., 45% obtained a complete remission compared to 27% in the VMP arm. The overall survival and progression free survival also were significantly better in the CHOP treated patients.(155) This study demonstrated that dose-reductions may jeopardize the effectivity of both CHOP and other regimens.

From these randomized studies it can be concluded that the standard chemotherapy regimen for elderly patients with an aggressive non-Hodgkin's lymphoma is full dose CHOP. A CR-rate of 47-60% can be attained. The survival of different age groups is in most studies identical (if reported), so age as such is no reason to withhold multidrug chemotherapy.(151, 154, 156, 157) Although the occurrence of hematologic, infectious and cardiac complications due to the anthracyclin is significant in the elderly patients, attenuation of the chemotherapy scheme reduces effectiveness. Therefore, attempts should be made to maintain the dose-intensity of CHOP, while reducing toxicity.

6.4. Hematopoietic growth factors.

In 1966 two research groups discovered that colonies of hematopoietic cells could develop in the presence of a medium with tissue extract.(158, 159) These colony-stimulating factors could later be isolated and produced using recombinant-DNA-techniques.(160) The myeloid hematopoietic growth factors are glycoproteins that stimulate the proliferation of bone marrow progenitor cells and their maturation into fully differentiated circulating blood cells. This was demonstrated in vitro and later confirmed in vivo.(161-163) The human recombinant granulocyte-macrophage colony-stimulating factor (rhGM-CSF) and granulocyte colony-stimulating factor (rhG-CSF) were developed in order to reduce chemotherapy induced neutropenia. Relatively shortly after the cloning of the genes the recombinant products became commercially available. In 1991 the United States Food and Drug Administration (FDA) approved their use.

Several phase I/II studies confirmed the effectiveness of these new colony-stimulating factors in stimulating neutrophil proliferation and function after standard or high dose chemotherapy.(164-171) GM-CSF and G-CSF also improved leucocyte recovery after high-dose therapy and bone marrow transplantation.(172-174)

The first randomized placebo controlled study with G-CSF was initiated in patients receiving standard chemotherapy for small cell lung cancer (SCLC). Patients that developed neutropenic fever were withdrawn from the study and received G-CSF after the next cycles. The primary endpoint was the incidence of neutropenic fever. After the first cycle 57% of placebo receiving

patients and 28% of the patients receiving G-CSF had fever with neutropenia. The mean number of days of hospitalization and the mean number of days of antibiotic use were reduced by approximately 50%. The rate of culture confirmed infections was also 50% reduced, from 13.3% in the placebo group to 6.5% in the G-CSF group.(175) The benefit of G-CSF was confirmed in a second randomized study in SCLC patients.(176)

A significant reduction in severe neutropenia and neutropenic fever was also observed in NHL patients treated with P-VABEC and G-CSF, compared to the control group without G-CSF support. However, the number of culture confirmed infections, days of i.v. antibiotics and hospitalization were not significantly reduced. In the control group more delay of chemotherapy cycles was necessary, due to neutropenia. No difference in response or survival was reported. The only side effect of G-CSF was musculoskeletal pain in 17% of the patients, easy controlled with simple analgesics.(177) Clinical benefit of GM-CSF after modified COP-BLAM chemotherapy for NHL was observed in another study: a decreased incidence of infections, decreased i.v. antibiotics and decreased duration of hospitalization were reported. Moreover, in the high-risk patients the CR-rate was significantly higher. This did not result in a difference in survival.(178)

Thus, hematopoietic growth factors might contribute to maintain dose-intensity by reducing the treatment related neutropenia and associated infections, which usually result in dose-reductions or delays of chemotherapy cycles. It has not been shown that they could also improve response rate and survival. Therefore, more randomized studies were needed to examine the role of hematopoietic growth factors on the CR-rate, disease-free and overall survival.

6.5. Dose intensity in elderly patients.

For elderly patients who can possibly tolerate multidrug chemotherapy it might be an option to diminish the resulting neutropenia by the use of recombinant colony-stimulating factors, such as G-CSF. Elderly patients encounter the most side effects following chemotherapy, especially bone marrow suppression. The first report in elderly patients (60-70 years) demonstrated that G-CSF may indeed reduce the duration of treatment related neutropenia resulting from a CHOP-like regimen.(179) The GELA performed a small phase II study with G-CSF and a CHOP-like regimen in patients 70 years or older. Compared to historical controls severe infectious complications, infection rate, hospitalizations and treatment related deaths were lower.(180)

A randomized trial investigating the role of granulocyte colony stimulating factor (G-CSF) as an adjunct to etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisone and bleomycin (VNCOP-B) chemotherapy in elderly patients showed that infection and neutropenia rates were reduced with the use of G-CSF. The CR-rate in the G-CSF arm was 60% compared to 58% in the control arm. No difference was observed between the age groups below and above 70 years. Relapse free survival and overall survival were similar in the two treatment arms. A significant difference in neutropenia was observed. Clinically relevant infections in the G-CSF arm were

infrequent (5%), and only mild. In the control arm 21% of patients experienced a relevant infection, a third of these infections required parenteral antibiotics and/or hospitalization. The dose intensity in both arms was respectively 95% versus 85%, but this was not statistically significant. G-CSF was well tolerated.(156) The GELA also reported less severe neutropenia, less infections and a better relative dose intensity, but no difference in CR-rate or survival with prophylactic G-CSF with the LNH-84 regimen.(181)
The German High-Grade Non-Hodgkin Lymphoma Study Group was the first to try to increase the dose intensity of CHOP above the standard dose in elderly patients, with remarkable results. This study in 698 patients 61-75 years of age had a 2 x 2 factorial design and investigated whether reduction of dose interval (CHOP-14), addition of etoposide (CHOEP) or both would improve outcome (CHOEP-14). With a median observation time of 58 months the CHOP-14 was superior to CHOP-21 in CR-rate, event-free survival and overall survival: CR-rate 76% vs 60%, 5-year EFS 44% vs 33% and 5-year OS 53% vs 41%. Toxicity was not enhanced by the interval reduction. The addition of etoposide (CHOEP-21) resulted in comparable results as CHOP-14, but at the cost of more toxicity, especially thrombocytopenia and infections. CHOEP-14 was even more toxic in these elderly patients, and resulted in more therapy related deaths and frequent treatment delays.(29)

In the 2000 Update of the ASCO guidelines for the Use of Hematopoietic Colony-Stimulating factors the routine use of CSF is considered to be not justified, because they have not shown to have a positive impact on disease-free and overall survival. In special circumstances, such as the treatment of elderly patients, CSF might help to complete the chemotherapy regimen, but a benefit in clinical outcome has not been observed.(182) The National Comprehensive Cancer Network advisory panel for the guidelines for the management of older individuals has recommended CSF in persons 70 years or older who are receiving moderately toxic chemotherapy, such as CHOP.(183, 184) The EORTC Cancer in the Elderly Task Force guidelines for the use of CSF in elderly patients with cancer recommended the use of prophylactic G-CSF to support the administration of planned doses of chemotherapy on schedule and to reduce the incidence of febrile neutropenia and infections.(185) Secondary prophylaxis, i.e. G-CSF administration with the chemotherapy cycles following the first episode of febrile neutropenia is not recommended. The major risk for febrile neutropenia occurs during the first and second course of chemotherapy.(186)
The administration of G-CSF has recently be simplified. The standard daily sc. dosing is no longer necessary since the development of a polyethylene glycol modified filgrastim (pegfilgrastim). This has resulted in decreased renal clearance and increased plasma half-life compared to filgrastim, and a longer pharmacologic effect. A single injection pegfilgrastim per chemotherapy cycle achieved the same effect as daily filgrastim injections.(187) Pegfilgrastim is cleared from the circulation by neutrophils and their precursors.(188) A small study in elderly patients treated with CHOP reported a similar duration of grade 4 neutropenia with filgrastim and pegfilgrastim. The incidence of febrile neutropenia was 10%.(189)

6.6. Immunotherapy.

Two multicenter randomized studies recently demonstrated a significant improvement in outcome of DLBCL with the addition of the chimeric anti-CD20 monoclonal antibody rituximab to CHOP (R-CHOP). The first study from the GELA in patients 60-80 years old observed an improvement of CR-rate from 63% (CHOP) to 76% (R-CHOP), a 2-year event-free survival of 38% (CHOP) versus 57% (R-CHOP) and a 2-year overall survival of 57% and 70% respectively.(27) Longer follow-up confirmed that this result was maintained over time: 5-year EFS 29% versus 47% and 5 year OS 45% versus 58% in CHOP and R-CHOP respectively.(190)

In this study 66% of the 399 lymphomas expressed bcl-2, an adverse prognostic marker. The improvement in event-free survival by addition of rituximab was demonstrated in the bcl-2 positive patients, while the results of the bcl-2 negative patients were not different with R-CHOP compared to CHOP.(191)

In the USA a large multicenter study with a 2 x 2 factorial design has been performed which addressed the role of rituximab both in induction therapy as in maintenance in patients >60 years old. The administration of rituximab in the induction scheme was different from the GELA regimen. The induction therapy results were influenced by the maintenance treatment. The addition of rituximab in induction or as maintenance improved the time to treatment failure significantly. Maintenance rituximab after R-CHOP did not prolong the time to treatment failure.(192)

The improvement of outcome by rituximab combined with standard chemotherapy has also been observed in a study in patients < 60 years, with low-risk diffuse large cell lymphoma (The Mabthera International Trial (MInT).(28)

6.7. Treatment for limited stage DLBCL.

The patients with stage I (and II) disease might benefit from a different approach. Up to 20 years ago radiotherapy was the treatment of choice. Although cure was achieved in a proportion of patients, relapse occurred in more than 50% of patients. This relapse usually was found outside the irradiated area, suggesting subclinical disseminated disease was present.(193, 194) Combined treatment of three or four chemotherapy (CHOP) cycles followed by involved field radiotherapy became standard treatment.(195) An alternative treatment strategy is full-dose chemotherapy without additional radiotherapy. However, combined modality treatment had a better outcome in a large randomized study. The 5-year progression-free survival was 77% in the CHOP plus radiotherapy treated group compared to 64% in the chemotherapy treated group. Overall survival was 82% versus 72%. Serious toxicity also was lower in the combined modality group.(196) A longer follow-up of this study observed that after 7 years the difference between the 2 treatment arms was no longer present.(197)

6.8. Palliative treatment.

The patients that have contraindications for a multidrug chemotherapy regimen should receive palliative treatment. Localized radiotherapy on symptomatic lesions may then be the treatment of choice. It is questionable if low-dose chemotherapy is of benefit, considering the risk of toxicity. The best palliation is cure of disease, but if a concomitant illness is a contraindication for chemotherapy treatment the primary goal is retaining a good quality of life. More studies to the patients' perception of their quality of life are necessary, in both studies with curative intent as in studies for palliative treatment.

7. Prognostic factors.

Age is recognized as an important negative prognostic factor. However, more factors have been analyzed that may predict outcome of NHL. The adverse prognostic significance of an aggressive growth pattern has been recognized already decades ago.(1) The importance of histology for the outcome resulted in the three malignancy grades of the Working Formulation.(7) In recent years more specific histologic entities proved to be of prognostic significance.(9, 25) Morphology is still the basis for the diagnosis of lymphomas. The use of immunophenotyping has greatly improved the diagnostic process for several entities, for example for mantle cell lymphoma.(198, 199) Several studies have shown that immunophenotyping may disclose prognostic variables, such as Ki-67, a marker for the proliferation rate in diffuse large B-cell lymphoma and mantle cell lymphoma.(200, 201)

One of the important adverse prognostic parameters of NHL is an elevated serum lactate dehydrogenase (LDH) at presentation.(202, 203) The performance status is another prognostic variable, and so is the tumor burden. The tumor burden is represented as the stage of disease, a bulky mass, the number of extranodal sites or a combination of these. Several prognostic systems were based on a multivariate analysis of prognostic variables in clinical studies.(204-207) An easy-to-use prognostic system based on a multivariate analysis of the results of 2000 patients with an aggressive NHL treated with a doxorubicin containing regimen was designed in 1993. In this International Prognostic Index (IPI) five adverse prognostic factors were recognized: an elevated serum LDH, stage III or IV disease, more than one extranodal localization, a WHO performance score >1 and age >60 years.(84) A combination of these factors resulted in four risk groups. In the subgroup analysis of patients above 60 years, an elevated serum LDH, a WHO performance score >1 and stage III or IV disease were the three adverse prognostic factors (table 6). The IPI was based on a large group of patients with predominantly B-cell lymphomas. It also predicted the chance of survival for a group of patients with peripheral T-cell lymphoma.(208) The IPI proved

also to be useful as a prognostic system for follicular lymphoma.(209, 210) However, only a small proportion of the patients with follicular lymphoma are high risk. Recently a prognostic score for follicular lymphomas has been published, the Follicular Lymphoma International Prognostic Index (FLIPI).(211)

Table 6. **International Prognostic Index.**

Risk factors:

Age: ≤ 60 vs. > 60 years
Serum LDH: ≤ 1x normal vs. > 1x normal
Performance status: 0 or 1 vs. 2-4
Stage: I or II vs. III or IV
Extranodal involvement: ≤ 1 site vs. > 1 site

Risk group	No of risk factors	CR-rate (%)	5-yr survival (%)
All patients			
Low	0 or 1	87	73
Low intermediate	2	67	51
High intermediate	3	55	43
High	4 or 5	44	26
Age-adjusted index, patients > 60			
Low	0	91	56
Low intermediate	1	71	44
High intermediate	2	56	37
High	3	36	21

Extranodal involvement did not retain independent prognostic significance in the age-adjusted index.

In the future, tumor-related variables will probably replace the current clinical prognostic factors. Results from molecular analysis, tumor proliferation index, and adhesion molecule expression were found to be significant in small studies, but they are not routinely performed.(212, 213) Using the DNA micro-array technique different gene expression profiles could be recognized which correlated with a different prognosis.(23, 57) The large group of diffuse large B-cell lymphomas could be subdivided in germinal center type and activated B-cell type. Micro-arrays however are not yet available for routine clinical practice. The germinal center phenotype could also be

recognized by bcl-6 and CD10 expression. Sequential addition of bcl-2 expression and germinal center phenotype improved the risk stratification of DLBCL.(47) However, another study could not confirm the prognostic significance of immunophenotyping profiles.(58) Probably, a selective set of genes expressed could predict outcome of treatment of DLBCL.(214)
Elderly patients might have a different genetic profile, and therefore have a different outcome. A study of the prognostic significance of bcl-2 and p53 overexpression in relation to age failed to confirm this in patients > 65 years, while it did confirm its significance in the younger patients.(60)
The currently in use prognostic system, the IPI, is based on a limited number of clinical factors. A prognostic system based on tumor specific markers should be developed. Such a tool may enable the clinicians to choose the best treatment for the individual patient.

In elderly patients the chronological age and performance status are important factors to predict treatment related mortality.(157) (215) The performance status can be influenced by the chronological age. In retrospective studies in elderly patients, but also in prospective studies, selection of patients is very common. Information about the reasons to refrain from curative therapy are scarce. Less than 50% of the patients 70 years or older with aggressive lymphoma were treated with an anthracyclin based regimen.(85)
Different opinions exist as to what age a patient is considered “elderly”. The lower limits in studies for elderly patients differ from 60 years, 65 years or 70 years. In a population based lymphoma registry in the Netherlands a decreased CR-rate was observed in patients with DLBCL 65 years or older.(216)

It should be mentioned that some special sites of involvement of NHL carry an extra poor prognosis.
The primary central nervous system (CNS) lymphoma occurs at a median age of 60 years. Its incidence increased gradually over the last 30 years. The therapy of choice is based on high-dose intravenous methotrexate and consolidation with whole brain radiotherapy. Patients aged 60 years or older encountered a great risk of late toxicity of the radiotherapy.(217) Palliative therapy with corticosteroids only or radiotherapy only is not effective and results in early death due to progressive disease within the CNS.
Testicular lymphoma usually occurs in elderly men. The median age at presentation is > 65 years. Standard treatment of limited stage disease with CHOP and radiotherapy results in relatively high relapse rates, especially in the contra-lateral testis and the CNS. Prophylactic intrathecal chemotherapy and scrotal radiotherapy is recommended. Advanced disease (stage III and IV) has a poor outcome.(218-220)
In conclusion, aggressive NHL in elderly patients has some specific characteristics, and its treatment may be hampered by several problems. However, chronological age is no reason to

refrain from adequate chemotherapy. The general condition of the individual patient, perhaps simply measured by the performance status, can predict the risk of treatment related morbidity and mortality. Contraindications for CHOP-like regimens are decreased cardiac function, impaired liver- and kidney function and impaired mental functioning. With adequate support during therapy, including instruction of family-members and other close relatives, many patients may benefit from the therapy.

8. Relapsed lymphoma.

In the last decade the standard treatment of refractory or relapsed diffuse large B-cell lymphoma has become high-dose therapy followed by autologous stem cell transplantation.(221, 222) This treatment is usually reserved for chemotherapy sensitive patients. It is too toxic for most patients above 65 years. Indeed, treatment related toxicity in patients undergoing autologous stem cell transplantation is already increased more than twofold in patients aged 50 or older.(223)

Patients with a chemotherapy refractory lymphoma, or patients older than 65 years have a poor prognosis. Standard dose therapy may result in a temporary disappearance or decrease of tumor, but second relapse or progression usually occurs within 2 years. Several chemotherapy regimens for relapsed or refractory lymphoma have been published. One of the frequently used regimens is DHAP (dexamethasone, cytarabin and cisplatin).(224) It is a quite toxic regimen. Myelosuppression, often complicated by neutropenic fever is an important side effect. Other commonly encountered toxicities result from the cisplatin, i.e. renal insufficiency, neurotoxicity and ototoxicity. In the PARMA study 6 cycles resulted in an event-free survival at 5 years of 12%.

IMVP-16 (ifosfamide, methotrexate and VP-16), MIME (methyl-gag, ifosfamide, methotrexate and etoposide), CAMP (lomustine, cytarabine, mitoxantrone and prednisone), EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) and ESHAP (etoposide, methylprednisolone, cytarabin and cisplatin) are among the combination chemotherapy regimens that have been investigated in phase II studies.(225-229) A complete remission was obtained in 27-37%, the median survival was 6-15 months.

Daily oral administration of etoposide has been studied in a group of elderly patients with relapsed lymphoma. This resulted in a complete remission in 20% of the patients. The median survival was 14 months.(131)

It can be concluded that second-line chemotherapy is not curative without high-dose therapy. For elderly patients the risk of toxicity of a palliative treatment is very important, and the quality of life should be maintained as long as possible. As no regimen is clearly superior to another, and no phase III studies have been performed, a regimen with a low toxicity profile should be proposed to elderly patients.

9. Quality of life.

The clinical response of anti-cancer treatment has historically been the only endpoint. This is clearly a very important outcome measurement, but the influence of treatment on the well-being of the patients deserves also attention. The last decades the interest in quality of life issues has gradually increased. Health related quality of life (QoL) refers to the physical, emotional and social domains of health. Health can be measured by objective assessment of functioning, but is also valued by subjective perceptions. The subjective perceptions may differ between subjects, depending on expectations and coping strategies, so the same objective health status may result in different experienced QoL. It has been documented that the QoL can not be accurately determined by doctors, but has to be measured by the patients themselves.(230, 231)
The European Organization for Research and Treatment of Cancer (EORTC) developed a questionnaire for use across many different cancer groups: the QLQ-C30.(232) Supplementary modules for specific diseases were also developed. A similar QoL instrument is the Functional Assessment of Cancer Therapy-General (FACT-G).(233) Both questionnaires consist of several subscales for different domains.
A very simple questionnaire is the EuroQol-5D. It measures 5 dimensions of health: mobility, self-care, daily activities, pain and anxiety, in 5 questions. The answers to the 5 questions are transformed into a total index score. This score can be used as a utility value to calculate quality adjusted life years (QALYs).(234)

Generally, if the expected outcome of an intensive therapy is good, a temporary increase of symptoms due to the treatment is accepted relatively easy. However, if a new therapeutic regimen has an equal outcome, but less side effects, the new therapy is the regimen of choice. If the outcome of treatment is less predictable, and the benefit of therapy less clear, the effect of treatment on the quality of life might be important in treatment decisions.
The majority of elderly patients with an aggressive lymphoma is not cured. Even if their condition is well enough to undergo standard dose chemotherapy the 5-year survival rate is less than 40%. Toxicity is usually higher than in younger patients. The impact on the subjectively perceived QoL during chemotherapy treatment may also be more pronounced in elderly patients. However, information on the effect of standard anti-lymphoma treatment is lacking.

10. Cost of treatment.

The demand on the health care budget increases steadily, due to an ageing population and new but expensive therapies. This results in increasing concern over the high cost of health care between policy makers. An efficient use of medical resources for lymphoma treatment is therefore necessary. Health economics focuses on analyses of treatments to determine which one is most cost-effective. The most simple technique of cost analysis is *cost-minimization*, in which it is assumed that outcome of two treatments is the same, and therefore a cost-minimization analysis focuses on finding the most inexpensive treatment. In *cost-effectiveness* analyses, both the cost as well of the outcomes of two treatments are being considered. A *cost-utility* analysis is a form of cost-effectiveness analysis, particularly focusing on the quality of the outcome, and usually applied in order to determine quality adjusted life years (QALYs). Life years gained are corrected for the quality of life of those years. *Cost-benefit* analysis expresses the additional life years in a certain price. Economic evaluations frequently use modeling approaches in order to estimate whether a new treatment alternative might be cost-effective. However, these modeling approaches require clinical and cost data that are representative for standard clinical practice.

Until recently information on the costs of standard care of patients with an aggressive non-Hodgkin's lymphoma was virtually non-existent, since CHOP chemotherapy had been used for decades and was not expensive as compared to other treatment regimens for cancer. The first studies on costs of lymphoma treatment appeared 10 years ago when new therapies and costly supportive care were upcoming. Particularly the costs and benefits of growth factor support and stem cell transplantation were evaluated in several studies.(179, 235-239)

The costs of treatment of aggressive NHL (including diagnosis and follow-up) in the context of a clinical trial compared to standard local practice were investigated in both younger and elderly patients in the Netherlands.(240) The costs of the diagnostic phase were slightly higher in clinical study patients. Elderly patients received more chemotherapy cycles if included in a clinical trial (not significant), and so had higher treatment costs. Generalizations of the study results were however hampered by the small patient numbers. The outcome of treatment was not studied, so cost-effectiveness could not be analyzed.(240)

The use of hematopoietic growth factors could increase the costs of treatment considerably. However, their use could have potential benefits. Firstly, the outcome of treatment could be better if administration of planned chemotherapy cycles could result in better response rates and survival. Secondly, less neutropenic fever could prevent hospital admissions and antibiotic therapies, and so save costs. Finally, if less infections would occur the quality of life of the patients

could improve. Quality adjusted life years (QALY's) could be determined. A cost-benefit analysis of prophylactic G-CSF with CHOP chemotherapy, that took into account costs from a societal perspective demonstrated a net increase of costs.(241) A small study (23 patients) investigated the clinical benefit and cost-effectiveness of G-CSF in patients aged 60-70 years with aggressive NHL. The response rate did not improve by the administration of G-CSF, but delay of chemotherapy cycles, grade III and IV granulocytopenia and severe infections were reduced. The addition of G-CSF resulted in an increase of the costs of 5000 ECU per patient, an increase of 60% compared to standard treatment.(179) An economic model calculated that the theoretical incremental cost per life year saved was $ 3300.(242)

It is important to realize that clinical effectiveness is the goal of any treatment, and higher costs should not prohibit the use of active therapies. However, economic analyses of new treatments are useful and inevitable, given the limited resources available. The combination of clinical effect, effects on quality of life and the resulting costs give an indication whether the new treatment is worthwhile.

11. History of clinical lymphoma studies in the Netherlands.

In the Netherlands the diagnosis non-Hodgkin's lymphoma is made in 2200 patients a year.(243) Fifty percent of the patients is older than 65. The diffuse large B-cell lymphoma is the most frequently diagnosed subtype (30% of cases).

In 1988 a prospective randomized multicenter study was initiated to investigate the efficacy and tolerance of CHOP versus CNOP. This study included 157 patients aged 60 to 84, and was finished in 5 years. It confirmed the superiority of doxorubicin 50 mg/m^2 above mitoxantrone 10 mg/m^2.(151) In this CNOP/CHOP study the chemotherapy had been administered every 4 weeks. The results were very encouraging, with 42% of the patients treated with CHOP being alive at 3 years, a relative dose intensity of 92% and an acceptable toxicity. This first Dutch multicenter lymphoma study also showed that a large study with participation from both university and community hospitals could be performed well and finished in a reasonable time.

In 1994 the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) initiated a phase III randomized multicenter study for elderly patients with aggressive NHL, the HOVON-25 study. The main question was if G-CSF support could maintain the dose intensity of standard CHOP, administered every 3 weeks, and so result in a better response rate and survival. Financial support

from the Dutch ministry of Health enabled the HOVON together with the institute of Medical Technology Assessment (iMTA) to include a quality of life and cost analysis. In September 2000 the accrual of the clinical study was completed. The results of the study are the main subject of this thesis.
The preliminary results of two large studies have been the basis of the next question, which is currently investigated in the subsequent HOVON study for elderly patients with diffuse large B-cell lymphoma, the HOVON-46 study. The complete results of these two studies that each showed an improved survival of the study-arm compared to standard CHOP have now been published.(27, 29) The German study group observed an improved response rate and survival with CHOP administered at 2 weeks (CHOP-14), while the French GELA group observed an almost similar improvement of response rate and survival with Rituximab-CHOP, while the addition of rituximab did not increase the toxicity of CHOP. The aim of the current HOVON study is to determine if addition of rituximab to CHOP-14 can improve the response rate and survival compared to CHOP-14.

This thesis describes the results of the HOVON-25 study, in which CHOP is compared with CHOP + G-CSF (chapter 2). The influence of CHOP-chemotherapy on the quality of life of elderly patients is the subject of chapter 3. In chapter 4 the costs of treatment of elderly patients with CHOP and G-CSF are presented. For patients with a relapsed lymphoma that do not qualify for re-induction followed by high-dose therapy with stem cell support we developed a regimen combining etoposide, mitoxantrone and prednisone (EMP). The results of this regimen are the subject of chapter 5.

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CHOP COMPARED WITH CHOP PLUS GRANULOCYTE COLONY-STIMULATING FACTOR IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA.

Chapter 2

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Abstract

Purpose: To investigate whether the relative dose-intensity of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy could be improved by prophylactic administration of granulocyte colony-stimulating factor (G-CSF) in elderly patients with aggressive non-Hodgkin's lymphoma (NHL).

Patients and methods: Patients aged 65 to 90 years (median, 72 years) with stage II to IV aggressive NHL were randomly assigned to receive standard CHOP every 3 weeks or CHOP every 3 weeks plus G-CSF on days 2 to 11 of each cycle.

Results: In 389 eligible patients, the relative dose intensities (RDIs) of cyclophosphamide (median, 96.3% v 93.9%; P = .01) and doxorubicin (median, 95.4% v 93.3%; P = .04) were higher in patients treated with CHOP plus G-CSF. The complete response rates were 55% and 52% for CHOP and CHOP plus G-CSF, respectively (P = .63). The actuarial overall survival at 5 years was 22% with CHOP alone, compared with 24% with CHOP plus G-CSF (P = .76), with a median follow-up of 33 months.

Patients treated with CHOP plus G-CSF had an identical incidence of infections, with World Health Organization grade 3 to 4 (34 of 1,191 cycles v 36 of 1,195 cycles). Only the cumulative days with antibiotics were fewer with CHOP plus G-CSF (median, 0 v 6 days; P = .006) than with CHOP alone. The number of hospital admissions and the number of days in hospital were not different.

Conclusion: In elderly patients, G-CSF improved the RDI of CHOP, but this did not lead to a higher complete response rate or better overall survival. G-CSF did not prevent serious infections.

Introduction

The survival of elderly patients with aggressive non-Hodgkin's lymphoma (NHL) is relatively poor.(1-5) Age older than 60 years is an adverse prognostic variable of the International Prognostic Index.(6) Several age-dependent factors are co-morbidity, altered drug pharmacokinetics, reduced tissue tolerance, attenuated dose-intensity of chemotherapy, and different intrinsic susceptibility of NHL to chemotherapy. Attempts have been made to design less toxic, still effective treatment for elderly patients. In general, these regimens have resulted in a lower efficacy compared with standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) treatment.(7-17) However, even with CHOP, the results in elderly patients are inferior to those in younger patients. This may be explained by the clinical practice to reduce the dose-intensity of CHOP in order to

prevent leucopenia and infections in this fragile population. An alternative approach to avoid chemotherapy-induced leucopenia and infections is prophylactic treatment with granulocyte colony-stimulating factor (G-CSF).(18-21) Many clinicians nowadays routinely use prophylactic G-CSF to prevent infections and treatment delays in elderly patients who undergo chemotherapy.(22) However, the literature does not provide evidence for this practice.(23)

In a multicenter phase III study in elderly patients with aggressive NHL, the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) has investigated whether prophylactic G-CSF plus standard CHOP chemotherapy reduces the incidence and severity of neutropenia and infections. The main purpose was to maintain the relative dose-intensity (RDI) of CHOP at standard dose, and by doing so, to improve the response rate and the survival of these patients.

Patients and Methods

Patients 65 years of age and older, with a biopsy-proven, newly diagnosed aggressive NHL according to the Working Formulation, as defined at the start of the study in 1994, were eligible.(24) They were required to have stage II, III or IV disease and a cardiac left ventricular ejection fraction $\geq$ 45%. Patients were not eligible if they had lymphoblastic NHL, positive HIV serology, other malignancy except localized squamous skin carcinoma, abnormal liver or kidney function unless caused by NHL, previous indolent lymphoma, or CNS involvement.

The required staging procedure included complete physical examination, blood analysis, computed tomography (CT) of the chest and abdomen and bone marrow aspiration plus biopsy. The staging procedure was repeated after 3 cycles of chemotherapy and at the end of treatment.

All patients gave informed consent for study participation according to the regulations of the Dutch health authorities. The study was performed and evaluated by the independent Dutch-Belgian HOVON group according to the Helsinki agreement. The study investigators are listed in the Appendix.

Treatment Protocol

The standard treatment consisted of CHOP (750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine (maximum 2 mg) intravenously on day 1, and 50 mg/m^2 prednisone orally on days 1-5). Patients randomly assigned to receive CHOP plus G-CSF also received 300 μg filgrastim (Neupogen; Amgen, Thousand Oaks, CA) subcutaneously on days 2 to 11. No prophylactic antibiotics were allowed. The first CHOP cycle had to be full dose, irrespective of blood counts. A 3-week interval was standard. For patients in whom the WBC count was not $\geq$ 3.0 x 10^9/L, or in whom the platelets were less than 100 x 10^9/L by day 22, the next cycle was

postponed for one week. If the counts had not recovered at day 29, dose reduction was mandatory. The dose of cyclophosphamide and doxorubicin was reduced to 75% if the WBC count was 2.0 - 3.0 x 10^9/L with platelets $\geq$ 100 x 10^9/L. A dose reduction to 50% was instructed if the WBC count was 1.0 - 2.0 x 10^9/L or if platelets were less than 100 x 10^9/L. Cyclophosphamide and doxorubicin were not given if WBC were less than 1.0 x 10^9/L or platelets were less than 50 x 10^9/L. The doses of vincristine and prednisone were not reduced.
Patients with a complete response (CR) after three cycles of CHOP received 3 additional cycles. Patients with a partial remission (PR) after three cycles received an additional five CHOP cycles, while patients with progression discontinued protocol treatment. Patients with stable disease were allowed to discontinue protocol treatment or to continue with three more cycles of CHOP, to the discretion of the physician. Patients with residual lesions from bulky mass ($\geq$ 10 cm) at the end of chemotherapy received involved field radiotherapy.

Response Criteria

CR was defined as disappearance of all symptoms and signs, disappearance of all measurable lesions, normal lactate dehydrogenase (LDH) for at least 6 weeks, and no bone marrow infiltration. Patients with small (<1 cm) lymph nodes still present at the end of treatment who showed no progression after 4 months were also considered as having CR. PR was defined as a reduction of all measurable lesions by more than 50% and no new lesions. Stable disease (SD) was defined as not fulfilling the PR criteria and having no signs of progression. Progressive disease (PD) was defined as the occurrence of a new lesion or increase of the original tumor mass by more than 25%. Early death was defined as death during treatment or within 3 weeks after the last chemotherapy cycle, regardless of the cause.

Quality-of-Life Study

To assess the quality of life (QoL) the EuroQol questionnaire (5 dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression), the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire - C30 (EORTC QLQ-C30) and the Multidimensional Fatigue Inventory (MFI-20, a fatigue scale) were used.(25-27) After patients' approval to participate in this part of the study, the questionnaire was sent to their home addresses before start of treatment; after the second, fourth, and sixth CHOP cycle; and at 3, 6, 10 and 18 months after the completion of treatment.

Cost Analysis

Costs were calculated in a select group of 100 consecutive patients (50 CHOP, 50 CHOP plus G-CSF) from two university and 10 community hospitals, from random assignment until 3 years of follow-up. The real costs of hospital admissions, day care, and outpatient visits were assessed in two university and two community hospitals. The weighted mean was used as the cost per unit. We used standard prices for medication, diagnostic procedures including laboratory examinations, and home care.

Statistical Analysis

To calculate the required number of patients to be entered in the study, the CR rate and the overall survival at 4 years from randomization (OS_4) were the primary endpoints. It was expected that in the control arm with CHOP alone, the CR rate would be 55% and the OS_4 would equal 45%. With a two-sided significance level $\alpha = 0.05$ and a power $1 - \beta = 0.80$ the number of patients needed to detect a 15% (10%) increase in CR rate was 352 (792) and 344 (762) for OS_4.(28, 29)

The expected accrual rate was 75 to 100 patients per year, which would result in 375 to 500 patients after 5 years' accrual. With these numbers of patients, the power for the detection of an improvement of 15% would be 83 to 92%.

The eligible patients were analyzed according to the intention-to-treat principle (i.e, analyzed according to the treatment arm they were assigned to). The data were analyzed as of October 22, 2001.

Patient characteristics were compared between the two treatment arms using Pearson's chi-squared test in case of discrete variables, or the Wilcoxon rank sum test in case of continuous variables. End points in the study included RDI, CR rate, OS, event-free survival (EFS), progression-free survival (PFS) and disease-free survival (DFS).

The RDI of each drug in the CHOP regimen was calculated by dividing the received cumulative dose by the full dose the patient should have received during the treatment period. OS was calculated from the date of random assignment until death. Patients still alive at the date of last contact were censored. EFS was measured from randomization until there was no CR on protocol, relapse, or death from any cause, depending on which came first. Patients who did not achieve a CR on protocol treatment were considered to have experienced failure at one day after random assignment. PFS was determined from the date of randomization until disease progression or death from NHL (including death due to treatment of NHL). Patients who were still alive or died from a non-NHL-related cause were censored at the date of last contact or date of death, respectively. DFS was calculated from date of CR until relapse. Patients who died in CR, irrespective the cause of death, were censored at the date of death.

OS, EFS, PFS and DFS were estimated by the Kaplan-Meier method.(30) Kaplan-Meier curves were generated to illustrate differences between the two treatment arms, and the log-rank test was used to compare the survival curves.(31)

The RDI of cyclophosphamide and doxorubicin were compared between the two treatment arms using the Wilcoxon rank sum test.

The proportion of patients who achieved a CR on protocol in the two treatment arms were compared using logistic regression, and a 95% confidence interval (CI) for the difference was calculated. Univariate logistic regression was used to see whether there was a difference in CR rate between subgroups according to patient characteristics at diagnosis.

Univariate survival analysis was performed with Cox regression to determine differences in survival between subgroups.(32) The univariate analyses were performed unadjusted as well as adjusted, for the Age-adjusted Prognostic Index (AAPI) score, to see which variables contained additional information besides the AAPI.(6)

At registration, the following variables were included in the analysis of prognostic factors: treatment arm, sex, age (continuous as well as in 4 subgroups), World Health Organization (WHO) performance status (0 to 1 v 2 to 4), PA diagnosis, B versus T-cell, "B"-symptoms, Ann Arbor stage (2 v 3 to 4), bulky disease, LDH (normal v elevated), erythrocyte sedimentation rate (normal v elevated), bilirubin (≤ 18 v > 18 μmol/L), creatinine (normal v elevated), hemoglobin (Hb, anemia v normal; i.e, Hb $>$ 8.6 mmol/L for men and Hb $>$ 7.5 mmol/L for women), platelets (≤ 150 v $> 150 \times 10^9$/L), WBC count (4 to 10 x 10^9/L v lower or higher), polymorphonuclear neutrophils ($\leq 40\%$ v $> 40\%$), bone marrow involvement, number of extranodal sites (0 to 1 v $\geq$ 2), International Prognostic Index and AAPI (low v low-intermediate v high-intermediate v high). All reported P-values are two-sided, and a significance level $\alpha = .05$ was used.

Results

Patient Characteristics

Four hundred eleven patients from 57 hospitals in the Netherlands and Belgium were enrolled between August 1994 and September 2000. Central pathology review was completed in 80% (313/389) of the patients. The diagnosis of intermediate- or high-grade was made according to the Working formulation. In 10% of the cases a definitive subclassification between the Working Formulation groups D through H or J was not possible, due to small biopsies or disagreement between pathologists. At central review by the study coordinators, 22 patients were evaluated as ineligible because of stage I disease (n = 7), low-grade NHL (n = 5), poor cardiac status (n = 4), no NHL (n = 1 each: acute myeloid leukemia, myelodysplastic syndrome, Hodgkin's disease, no malignancy, renal insufficiency (n = 1), or administrative reasons (n = 1), and were excluded from further analysis. The remaining 389 patients were randomly assigned to CHOP (n = 192) or CHOP plus G-CSF (n = 197). All risk factors were balanced between the two treatment groups except for bulky disease, which was more prevalent in the CHOP plus G-CSF arm (P = .04; Table 1). The median age at random assignment was 72 years. According to the AAPI, 54% of patients had high-intermediate or high risk NHL.

Treatment and Dose-Intensity

Seventy-five 75% of the patients completed six or eight cycles of CHOP. In 32% of the patients, the scheduled treatment was prematurely stopped because of toxicity (13%), disease progression (9%), or other reason (Table 2). In eight patients randomly assigned to CHOP plus G-CSF, G-CSF was not given during 26 cycles because of bone pain, fatigue, patient refusal, or other reason.
The difference in the median RDI of cyclophosphamide was 2.4% (ie, 96.3% in patients treated with CHOP plus G-CSF, compared with 93.9% with CHOP alone; P = .01). For doxorubicin the difference in RDI was 2.1% (95.4 v. 93.3%, respectively; P = .04; Table 3).

Table 1. **Patient characteristics per treatment group**

	Allocated treatment					
	CHOP		CHOP + G-CSF		Total	
Characteristic	No. of patients	%	No. of patients	%	No. of patients	%
Total	192	-	197	-	389	-
Sex						
Male	109	57	107	54	216	56
Female	83	43	90	45	173	44
Age, years						
Mean	73		73		73	
SD	5		5		5	
Median	73		72		72	
Range	65-90		65-90		65-90	
Age distribution, years						
65-70	73	38	73	37	146	38
71-75	65	34	68	35	133	34
76-80	42	22	40	20	82	21
> 80	12	6	16	8	28	7
WHO performance status						
0-1	155	81	161	82	316	81
2-4	37	19	36	18	73	19
Ann Arbor stage						
II	48	25	49	25	97	25
III	33	17	45	23	78	20
IV	111	58	103	52	214	55
B-symptoms						
No	121	63	127	64	248	64
Yes	71	37	70	36	141	36
Bulky disease						
No	156	81	143	73	299	77
Yes	36	19	54	27	90	23
LDH						
Normal	72	38	79	40	151	39
Elevated	120	62	118	60	238	61

Table 1. **Patient characteristics per treatment group,** continued.

PA diagnosis (WF)						
Follicular large cell	9	5	15	8	24	6
Diffuse small cell	25	13	19	10	44	11
Diffuse mixed cell	21	11	23	12	44	11
Diffuse large cell	95	49	102	52	197	51
Immunoblastic	21	11	19	10	40	10
Burkitt	1	1	-	-	1	0
Unclassifiable	20	10	19	10	39	10
Immunological diagnosis						
B-cell	164	86	170	86	334	86
T-cell	14	7	15	8	29	7
Not known	14	7	12	6	26	7
No. of extranodal sites						
0-1	142	74	154	78	296	76
> 1	50	26	43	22	93	24
Age-adjusted IPI						
Low	22	11	21	11	43	11
Low-intermediate	63	33	71	36	134	34
High-intermediate	83	43	84	43	167	43
High	24	13	21	11	45	12

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; SD, standard deviation; WHO, World Health Organization; LDH, lactate dehydrogenase;WF, Working Formulation; IPI, International Prognostic Index.

Toxicity

Three-times-weekly CHOP therapy was generally well tolerated. Neutropenic fever (>38.5°C) was observed in 86 patients treated with CHOP and in 72 patients treated with CHOP plus G-CSF. The median duration of fever in these patients in all cycles together was 3 days (range 1 to 32) and 2 days (range 1 to 14), respectively (P = .04). One hundred eighty (15%) of 1,195 CHOP cycles were complicated by an infection with WHO grade 2 to 4, compared with 135 (11%) of 1191 CHOP plus G-CSF cycles (P = .007). The number of severe infections (WHO grade 3 to 4) was equal in both treatments (Table 4). The number of infectious complications decreased sharply beyond the first cycle (CHOP, 32% v CHOP plus G-CSF, 20%, P = .01) and second cycle (CHOP, 14% v CHOP plus G-CSF, 13%, P = .92). The lower incidence of grade 2 infections with CHOP plus G-CSF was associated with a significant reduction in antibiotic prescriptions. The median duration of antibacterial treatment was 6 days (range, 0 to 180) in patients treated with CHOP and 0 days (range, 0 to 126) in patients treated with CHOP plus G-CSF (P = .006). However, the number of days of hospital stay was equal with both treatments (ie, 6 days with CHOP (range, 0 to 111) and 5 days with CHOP plus G-CSF (range, 0 to 157); P = .40). The nonhematologic toxicity is shown in Table 5.

The observed toxicity was not influenced by age (Table 6). However, patients older than 80 years completed significantly less treatments as compared to younger patients due to toxicity, refusal, or death (43% v 80%; P < .001). The treatment-related mortality was 7.5% (29 patients), of which 17 cardiac deaths (Table 7).

Table 2. **Reasons to go off protocol treatment**

	Allocated treatment					
	CHOP		**CHOP + G-CSF**		**Total**	
Reason	No. of patients	%	No. of patients	%	No. of patients	%
Total	192	-	197	-	389	-
Protocol completion	131	68	135	69	266	68
Toxicity	30	16	21	11	51	13
Progression / relapse	12	6	22	11	34	9
Death	10	5	8	4	18	5
Refusal	4	2	6	3	10	3
No response after 3 CHOP	3	2	2	1	5	1
Protocol violation	1	1	2	1	3	1
Other	1	1	1	1	2	1

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor.

Response to Therapy

The overall response rate in patients treated with CHOP was 83%, compared with 85% in patients treated with CHOP plus G-CSF (P = .70). The CR rates were 55% and 52%, respectively (P = .63). The 95% CI for the difference of the CR rates is –12% to 8%. In 96% of the patients who attained at least a PR, this response was already achieved with 3 cycles. The number of CRs increased from 43% after 3 cycles to 53% after 8 cycles of CHOP or CHOP plus G-CSF with no difference between the treatment arms.

Table 3. **The relative dose intensity of CHOP (%)**

	Allocated treatment			
Agent	**CHOP**	**CHOP + G-CSF**	**Total**	**P**
Cyclophosphamide				
Mean	90.0	93.3	91.7	
SD	12.0	9.7	11.0	
Median	93.9	96.3	95.5	.01
Range	48.3 – 112	39.5 - 106	39.5 – 112	
Doxorubicin				
Mean	89.8	93.0	91.4	
SD	11.8	10.0	11.0	
Median	93.3	95.4	95.0	.04
Range	47.6 – 103	39.5 - 127	39.5 – 127	
Vincristine				
Mean	85.8	86.3	86.1	
SD	19.5	20.8	20.1	
Median	93.0	95.5	94.8	.60
Range	0.0 – 104	0.0 - 106	0.0 – 106	
Prednisone				
Mean	95.5	97.2	96.4	
SD	13.2	14.6	14.0	
Median	97.2	98.1	97.8	.18
Range	47.4 – 139	21.6 - 138	21.6 – 139	
CHOP				
Mean	90.3	92.5	91.4	
SD	12.0	10.7	11.4	
Median	93.4	95.1	94.6	P=0.12
Range	47.7 – 109	39.4 - 110	39.4 – 110	

NOTE. All values are percentages.

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor. SD, standard deviation.

Table 4. **Infections and use of antibiotics**

	CHOP*		**CHOP + G-CSF****		
	No. of patients	%	No. of patients	%	P
Infections WHO 2	144	12	101	8	.004
Days with antibiotics					
Median	8		7		.02
Range	2-39		1-66		
Infection WHO 3 to 4	36	3	34	3	.82
Days with antibiotics					
Median	8		10		.60
Range	1-69		2-42		

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; SD, standard deviation; WHO, World Health Organization toxicity grade.

* Total 1,195 cycles.

** Total 1,191 cycles.

Table 5. **Nonhematologic toxicity according to treatment group**

	WHO grade 2				WHO grade 3 to 4			
	CHOP*		**CHOP + G-CSF****		**CHOP***		**CHOP+G-CSF****	
Event***	No.of patients	%	No.of patients	%	No.of patients	%	No.of patients	%
Neurotoxicity	113	9	82	7	33	3	13	1
Nausea/vomiting	47	4	48	4	18	2	15	1
Diarrhea	25	2	9	1	2	<1	8	1
Oral toxicity	19	2	12	1	4	<1	2	<1
Cardiac toxicity	10	1	12	1	6	1	9	1
Hemorrhage	7	1	6	1	1	<1	-	-
Liver toxicity	3	<1	3	<1	1	<1	-	-
Bone pain	2	<1	28	2	-	-	3	<1
Renal toxicity	1	<1	3	<1	-	-	-	-
Allergy	1	<1	-	-	-	-	-	-
Other	118	10	89	7	30	3	23	2

Abbreviations: WHO, World Health Organization; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor.

* Total 1195 cycles.

** Total 1191 cycles.

*** Maximum WHO grade of adverse event per cycle.

Table 6. **Toxicity according to age group.**

Toxicity	Age (years) 65-70 (n=146)	71-75 (n=133)	76-80 (n=82)	>80 (n=28)	Total (n=389)	P
Infection*						
0-1	45	56	40	54	48	
2	41	31	40	25	36	.74
3	11	8	11	14	10	
4	3	5	9	7	5	
Side effects*						
0-1	45	41	40	43	42	
2	32	34	28	25	31	.30
3	20	19	27	21	21	
4	4	7	5	11	6	
Reason off protocol						
Toxicity	8	14	18	25	13	
Refusal	1	2	6	7	3	< .001
Death	4	2	6	18	4	
Number of cycles						
0-5	15	19	33	57	23	
6	29	34	37	29	32	< .001
7	2	3	1	-	2	
8	54	44	29	14	43	

Note. All values are percentages

* Maximum WHO grade observed during all cycles

Survival

With a median follow-up survival of 143 patients still alive of 33 months, 143 events occurred in the CHOP arm and 152 in the CHOP plus G-CSF arm. EFS at 5 years was not different between patients treated with CHOP (18%) or CHOP plus G-CSF (17%; P = .52). PFS was 24% and 25% in the CHOP and CHOP plus G-CSF arms, respectively (P = .65). DFS was 40% in patients treated with CHOP plus G-CSF, compared with 43% in the control group (P = .31). At 5 years, the OS was 24% in the CHOP plus G-CSF arm and 22% in the CHOP arm (P = .76; Fig 1). The actuarial survival curves for the AAPI subgroups are shown in Figure 2. There was no difference in death from NHL (78 with CHOP v 88 patients treated with CHOP plus G-CSF; P = .17; Table 7).

Table 7. **Causes of death**

	Allocated treatment					
	CHOP		**CHOP + G-CSF**		**Total**	
Cause of death*	No. of patients	Early death	No. of patients	Early death	No. of patients	Early death
Total	123	18	123	11	246	29
NHL	78	3	88	2	166	5
Infection	16	6	11	4	27	10
Cardiac	8	3	9	3	17	6
Other malignancy	3	-	6	-	9	-
Cerebral	2	-	2	-	4	-
Toxicity	3	-	-	-	3	-
Other	2	-	3	-	5	-
Not known	11	6	4	2	15	8

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin's lymphoma.

Prognostic Factors

Univariate logistic regression showed that B-symptoms, elevated bilirubin (both $P < .05$), stage III to IV, anemia, bone marrow involvement, more than one extranodal site and a higher AAPI score (all $P < .01$) were associated with a lower CR rate. Univariate Cox regression showed that elevated erythrocyte sedimentation rate, abnormal WBC count (both $P < .05$), higher age, WHO 2 to 4, B-symptoms, stage III to IV, elevated LDH, elevated bilirubin, anemia and a higher AAPI score (all $P < .01$) predicted for inferior OS.

Prophylactic G-CSF was not associated with an improvement of any of the end points, while a higher AAPI score predicted for worse outcome for both CR rate and OS. Therefore the univariate analyses were also performed with adjustment for the three factors of the AAPI (WHO 2 to 4, stage III to IV and elevated LDH) to find variables that were significant on top of the AAPI. Only variables that were significant in the unadjusted univariate analyses were included.

Older age ($P < .05$), bone marrow involvement, and more than one extranodal site (both $P < .01$) were associated with a lower CR rate. Adverse prognostic factors for OS were elevated bilirubin, anemia and abnormal WBC count (all $P < .05$) and higher age ($P < .01$) (Tables 8 and 9).

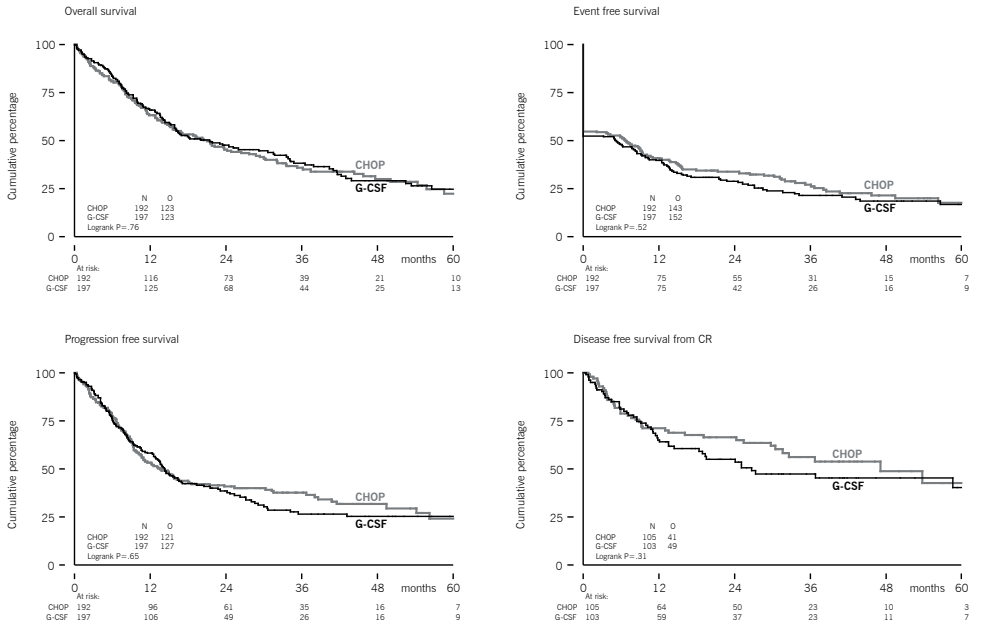

Fig 1. **Overall survival, event-free survival, progression-free survival and disease-free survival from complete response by treatment arm.**
CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin's lymphoma

QoL Assessment

One hundred sixty-two patients were asked to participate in the QoL study. Thirty patients refused (19%). They differed from the total study population only by the higher frequency of B-symptoms (36% v 26%). During the study period, 96% of the questionnaires were returned, and in the follow-up period, 88% were returned. In patients with progressive disease or relapse the questionnaire return rate decreased to 77%. Since there was no difference in QoL between both treatments, the results are combined. During treatment the EuroQol did not change (Figure 3). The mean QLQ-C30 scores for the different domains did not change in time. Patients with B-symptoms scored significantly lower before treatment on almost all scales. This difference was no longer present after four chemotherapy cycles. There was an inverse association between fatigue and hemoglobin level at all time points.

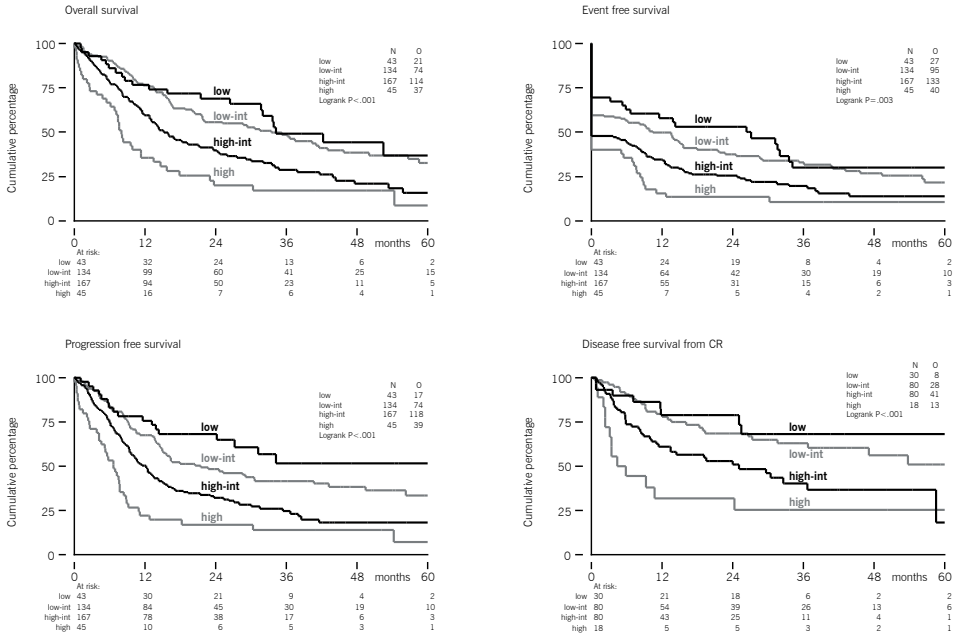

Fig 2. **Overall survival, event-free survival, progression-free survival and disease-free survival from complete remission per Age-adjusted Prognostic Index risk group**

During follow-up, the QoL scores were attributed to the different clinical outcomes: CR, PR or progression or relapse. Three months after completion of therapy, patients with PR or CR reported significantly higher levels of QoL compared with pretreatment and during-treatment values. Only the patients with progression or relapse reported a significant lower QoL. With longer follow-up, no major changes occurred in QoL.

Cost analysis

The mean total costs during treatment from the date of randomization were € 10,539.- (CHOP) versus € 16,382.- (CHOP plus G-CSF; $P < .01$; 95% CI of the difference € 3,107.- to € 8,578.-). The costs during follow-up amounted to € 9,235.- per patient, with a total follow-up of 3 years. The costs during the follow-up were highest for patients with progression or relapse (data not shown).

Table 8. **Adverse prognostic factors for CR and overall survival: Univariate logistic regression analysis of prognostic factors for CR, adjusted for AAPI.**

Characteristic	Odds Ratio	95% CI	P
CHOP + G-CSF	0.89	0.59 to 1.34	.58
Age*	0.96	0.92 to 1.00	.04
BM involvement	0.54	0.35 to 0.84	.006
>1 extranodal site	0.47	0.29 to 0.78	.003

Abbreviations: CR, complete remission; AAPI, Age-adjusted Prognostic Index; CI, confidence interval; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; BM, bone marrow
* the odds ratio corresponds to an increase of age with 1 year.

Table 9. **Adverse prognostic factors for CR and OS: Univariate Cox regression analysis of prognostic factors for OS from randomization, adjusted for AAPI.**

Characteristic	Hazard Ratio	95% CI	P
CHOP+G-CSF	0.93	0.73 to 1.20	.59
Age*	1.06	1.03 to 1.09	<.001
Bilirubin > 18 μmol/L	1.69	1.12 to 2.53	.01
Anemia**	1.34	1.01 to 1.77	.04
Abnormal WBC***	1.31	1.11 to 1.71	.05

Abbreviations: CR, complete remission; OS, overall survival; AAPI, Age-adjusted Prognostic Index; CI, confidence interval; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; BM, bone marrow CI: confidence interval

* the hazard ratio corresponds to an increase of age with 1 year;
** Hb < 8.6 mmol/L for men and < 7.5 mmol/L for women
*** < 4 or > 10 x 10^9/L.

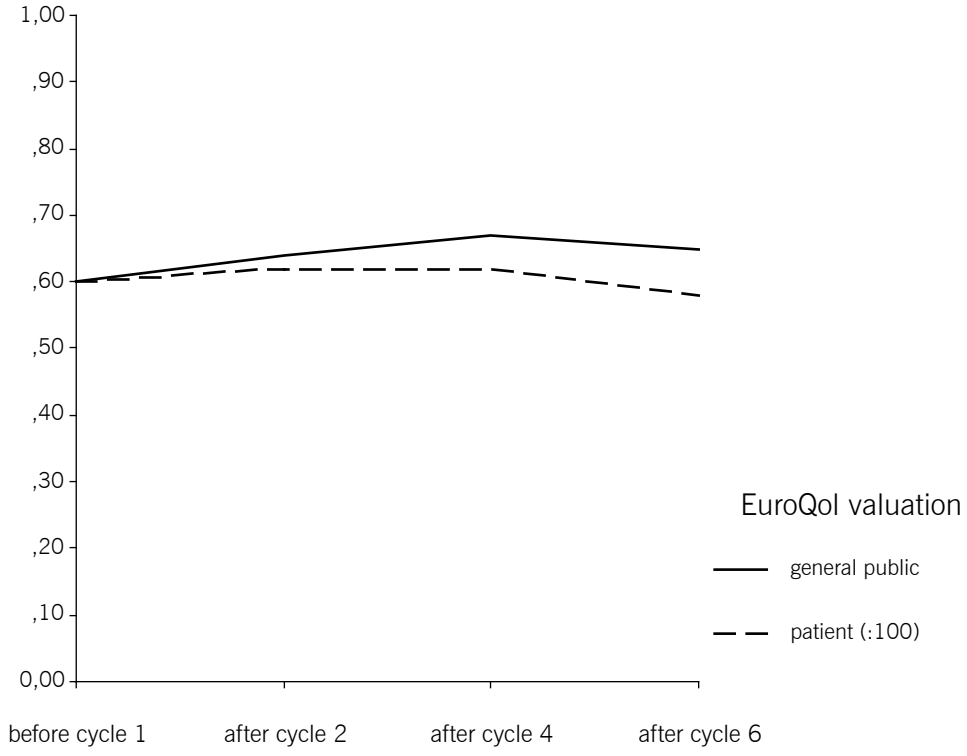

Fig 3. **Mean EuroQol score during treatment The general public score reflects the health utility index (range, 0 to 1) of the patients, as valued by the general public. The patient score is the value which patients attributed to their own health on a thermometer (range, 0 to 100)**

Discussion

CHOP chemotherapy in elderly patients is frequently accompanied by the risk of neutropenic fever. Because of the risk of severe morbidity and mortality in this population clinical practice is to postpone CHOP cycles or to reduce the dose in order to prevent (cumulative) toxicity. However, this may result in a lower dose-intensity of the required treatment. It has been shown that dose reduction of CHOP is associated with a lower response rate and a relatively poor OS.(3) Several studies have suggested that G-CSF improves the adherence to the chemotherapy schedule and minimizes dose modifications in elderly patients with NHL.(33, 34) Therefore, prophylactic treatment with G-CSF has become routine clinical practice in these patients.

This study was designed to evaluate whether standard prophylactic administration of G-CSF may indeed improve the probability that a potentially curative treatment such as CHOP is administered at the required dose-intensity, and whether this improves long-term OS and DFS.

Unexpectedly, with standard CHOP, the median RDI was greater than 90%, indicating that the need for dose reduction is relatively rare. With prophylactic G-CSF, the median dose of doxorubicin and cyclophosphamide increased by only 2.1% and 2.4%, respectively. This small increase of dose did not lead to a better response rate or OS. In a recently published study from the Nordic Lymphoma Group prophylactic G-CSF with CHOP or cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP) in elderly patients improved the RDI, but this did not result in a higher CR rate, longer time to treatment failure or better OS.(35)

An additional potential advantage of prophylactic use of G-CSF (ie, to reduce serious complications from neutropenia) was also not demonstrated. While G-CSF reduced the number of mild infections (WHO grade 2) and the use of antibiotics, the frequency of serious infections was identical. Moreover, the number of hospital admissions during chemotherapy was similar in both groups. Also, the toxic death rate (6%) with or without G-CSF was in accordance with other controlled studies.(13, 16, 22, 36)

In this study, there was no upper age limit. As expected, patients of higher age more often retracted from treatment before the completion of the planned treatment cycles. Prophylactic G-CSF did not influence this pattern, nor did G-CSF reduce the incidence of severe neutropenic fever in patients older than 70 years. Higher age proved to be a negative prognostic factor for OS, but not for PFS and DFS. Therefore, this observation seems to be the result of death causes not related to NHL.

In this fragile patient group, QoL is an important issue when deciding to administer chemotherapy. The QoL significantly improved during CHOP in patients with B-symptoms, and remained equal in all other patients. This implies that a poor QoL before start of CHOP is no reason to adjust treatment. G-CSF had no effect on the QoL. After completion of treatment most chemotherapy-related symptoms disappeared, and the patients' QoL improved rapidly.

Prophylactic G-CSF was not cost-effective. The number of hospital admissions was not reduced, while the use of antibiotics was marginally less. In economic studies, prophylactic G-CSF is cost-neutral at an infection incidence of 40%.(37, 38)

In conclusion, we could not demonstrate an improvement of OS with prophylactic G-CSF administration. It is, however, possible that a small difference between the arms may have been missed due to the sample size. The OS at 5 years was only 22 to 24%. The majority of the patients (67%) died from NHL. Prophylactic G-CSF did not prevent severe infections or lower the number of hospital admissions. Evidently, the high relapse rate indicates that the treatment of elderly patients with aggressive NHL should be reconsidered. Other modalities such as antibody therapy or intensification of CHOP are needed to improve the clinical outcome of NHL in these patients.(36, 39)

Appendix

The following persons and institutions participated in this HOVON study:

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CORRESPONDENCE AND REPLY

CHOP VERSUS CHOP PLUS GRANULOCYTE COLONY-STIMULATING FACTOR IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA.

Chapter 3

Alliot C.

In Reply
Doorduijn JK, Sonneveld P.

Journal of Clinical Oncology. 2005, in press

To the Editor:

I read with interest the article by Doorduijn and the HOVON group in the August 15, 2003 issue.(1) In a randomised study, the authors compared the CHOP regimen given every 3 weeks to the same regimen plus G-CSF in elderly patients with aggressive non-Hodgkin's lymphoma. The studied population aged from 65 to 90 (median, 72) appears older than that of previous comparable studies. The modest improvement in relative dose intensity (RDI) in the group with G-CSF lead logically neither to a higher response rate nor to a better overall survival. Patients older than 80 years completed significantly fewer treatments with 57% receiving less than 6 cycles and only 14% receiving 8 cycles. Treatment-related toxicity led to the death of 29 patients (7.5%), including 17 cardiac events. The first point to discuss is the ambitious goal of a 15% increase in complete response only by adding G-CSF. Because the RDI of cyclophosphamide and doxorubicin were of about 93% in the control arm, this strategy appears clearly insufficient in terms of efficacy. In line with this, the French multicenter trial of Coiffier and colleagues comparing CHOP to CHOP plus rituximab showed that more than 90% of patients received more than 90% of the planned dose while 43% had received G-CSF curatively after 8 cycles.(2) A retrospective study of patients aged over 65 years treated with CHOP before routine use of G-CSF showed that 65% of them received more than 90% of the planned dose although 21% received less than 75%.(3) Thus, a vast proportion of the younger patients do not beneficiate from G-CSF in terms of RDI. The RDI may depend not only on improvement in hematologic recovery but also on compliance favoured by various recent advances such as psychological support, long term venous access or recent molecules improving tolerance such as setrons or modern antidepressants. The present study confirms that nonhematologic toxicities become prevalent in patients aged over 70 and clearly unacceptable over age 80. A multicentre Spanish phase II study of CHOP with GM-CSF support previously showed a treatment-related mortality of 18% in patients over age 70 versus 0 in those aged 60 to 69 years.(4) In this study, mucositis has been observed in 21% of the cycles in patients younger than 70 years versus 42% in the older. In fact, standard full-dose CHOP represents an intensified therapy in this population given the numerous pharmacokinetic changes arising during ageing. Several mechanisms result in changes in the volume of distribution (Vd) of the drugs, including a loss of total body water, an increased total body fat, a decreased albumin by about 20% between 25 and 75 years.(5) Certain drugs, such as the anthracyclins, are intensively bound on the erythrocytes. Thus, the Vd may be also increased by anemia. There is a prolongation in the early distribution phase of doxorubicin in the elderly, leading to the persistence of high plasma concentrations and potentially favoring cardiotoxicity.(6) The aging of the kidneys results in a progressive decline of the glomerular filtration rate of 1 ml/min each year after age 40.(7) Thus, dose adaptation has been proposed for creatinine clearance lower than 60 ml/min.(8) Certain treatments of comorbid illnesses may interfere with chemotherapy, in particular

for cytochrome P-450 enzyme or conjugation reactions. These interactions may play a role in the case of cyclophosphamide which is extensively metabolised in the liver by the cytochrome P-450 isoenzymes CYP2B6, CYP3A4 and CYP2C.(9) For example, CYP3A4 can be induced by carbamazepin or phenytoin and inhibited by macrolides, fluvoxamine or antifungal imidazoles.(10) Moreover, numerous drugs such as warfarin, phenytoin, salicylates or tolbutamide may displace chemotherapeutic agents from albumin binding sites.(11) The importance of polypharmacy has been illustrated by a study at H. Lee Moffit Cancer Center revealing that 56% of the patients usually take more than 4 drugs.(12) On the other hand, a significant improvement in terms of survival can be obtained either by time intensification as shown by the German multicenter trial LNH-B using 2-weekly CHOP or by dose intensification in the French LNH-93-5 trial using 3-weekly ACVBP regimen (with doxorubicin, 75 mg/m2, cyclophosphamide, 1200 mg/m2).(13, 14)

Nevertheless, the median age were 67 and 65 years respectively and these strategies seem beneficial essentially in patients younger than 66 years because of toxicity.

In conclusion, this study confirms the limits of support with G-CSF. A number of measures could decrease toxicity such as adaptation of usual treatments, dose adaptation of cyclophosphamide according to creatinine clearance, correction of anemia by transfusion or erythropoietin. Given a half-life of about 19 days, albumin might be administered simultaneously to chemotherapy. Because cardiotoxicity is largely unpredictable and doxorubicin remains the key-drug, dexrazoxane should be administered before the cumulative dose of 300 mg/m^2. The only alternative to these measures would consist in exploring standard adaptations of CHOP within age brackets of less than 10 years. Obviously, standard full-dose CHOP should not be used in patients aged over 80.

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In Reply:

The HOVON study comparing CHOP q 3 weeks versus CHOP q 3 weeks plus G-CSF was initiated in 1994 to investigate if G-CSF support in elderly patients with aggressive non-Hodgkin's lymphoma (NHL) could achieve a higher relative dose intensity (RDI), resulting in a better outcome.(1) At that time, it was well known that elderly patients had a poor outcome with CHOP compared to younger patients.(2) Until then, many studies on elderly patients with aggressive NHL had focused on reducing toxicity, assuming that standard CHOP q 3 weeks was too toxic for most of the patients. Our study showed that standard CHOP q 3 weeks was tolerable for the majority of the elderly patients, using standard in- and exclusion criteria, provided that the criteria for dose reduction were strictly followed using a predefined algorythm. G-CSF could not improve the RDI by a large extent which was due to the higher RDI (> 90%) than expected in the standard treatment arm. This reflects the fact that the majority of patients, with a median age of 72 years, completed the planned schedule and chemotherapy dose without problems. The results of the study by Campbell et all were not yet published in 1994, but it showed that without a stringent algorithm on dose reduction a considerable number of their patients received less than 90% of the planned dose of chemotherapy.(3) In contrast, 43% of the patients > 80 years in our study completed six or more CHOP-cycles. Even then, higher age was an adverse prognostic factor for complete remission and overall survival. However, this was not related to increased toxicity or early death, and therefore we disagree with Dr. Alliot that age >80 is an absolute contraindication for full-dose CHOP.

The risk of toxicity of a chemotherapy regimen in elderly patients should be weighed against the morbidity and a short survival due to the disease if not treated with curative intent. The observed treatment-related mortality of 7.5% in our patient group with a median age of 72 years is in accordance with other studies.(4-6) The results of our quality of life analysis in this patient group do not suggest that the toxicity is unacceptable to these subjects.(7) Oral toxicity in our study was relatively rare: only in 2% of the cycles mucositis was observed.

As to the multiple age dependent factors that contribute to the increased toxicity of CHOP in elderly patients we agree with Dr. Alliot that changes in pharmacokinetics might be important. Reduced elimination and/or higher concentrations of active drugs may contribute to the increased toxicity in elderly patients, however it is no explanation for the lower CR-rate and higher relapse rate that are observed in elderly patients. In the literature there is no consensus as to pharmacokinetic alterations to explain increased toxicity in elderly patients. A prospective study in breast cancer patients treated with doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 i.v. observed no age-related differences in the clearance of these drugs, and no age-related trends in toxicity.(8) Indeed, pharmacologic factors that are not related to age are more likely to influence the toxicity of chemotherapy. For example, drugs which inhibit or induce the activity of cytochrome P-450 may

interfere with the cytotoxic effect of cyclophosphamide. Another factor contributing to differences in pharmacokinetics is the presence of polymorphism of several cytochrome P-450 enzymes.(9, 10) Taken together, age related differences of pharmacokinetics of doxorubicin and cyclophosphamide do not seem to have a dominant effect on the outcome of therapy, while comorbidity, concomitant drug use or genetic factors seem more important. Several recent studies have shown that standard or even more intensified treatment of aggressive NHL in elderly patients is feasible and results in a better outcome than with dose-reduced chemotherapy.(6, 11)

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SELF-REPORTED QUALITY OF LIFE IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA TREATED WITH CHOP CHEMOTHERAPY.

Chapter 4

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Abstract

We studied the impact of CHOP chemotherapy on the quality of life (QoL) of elderly patients with aggressive non-Hodgkin's lymphoma (NHL). 132 patients aged 65 or older, who participated in a randomized, multicenter trial, completed QoL questionnaires (EuroQol-5D, EORTC QLQ-C30 and MFI-20) on 8 predefined time-points before, during and following treatment.
At baseline, QoL was significantly better on almost all dimensions in patients with a lower compared to patients with a higher age-adjusted International Prognostic Index (aaPI). During treatment, physical and role functioning and global QoL deteriorated and fatigue increased in the lower aaPI group (all $P < 0.01$), whereas QoL of the higher aaPI group remained stable. During follow-up, the QoL was significantly better for patients in complete response (CR) or partial remission (PR) than for patients with progression/relapse. At three months after completion of therapy, the QoL of the lower aaPI group returned to pretreatment levels or better, while patients with higher aaPI showed a significant improvement in QoL compared to baseline levels. The effect of CHOP on the quality of life of elderly patients could be used in counseling this group of patients.

Introduction

The effect of chemotherapy treatment on the quality of life (QoL) is an important question for patients. For elderly patients this is even more important. Their general health often is impaired due to concomitant disease, and the functional status may deteriorate more from tumor symptoms. Side-effects due to chemotherapy on top of the impaired general condition may be tolerated poorly. However, few data are present on the effects of chemotherapy on QoL of elderly patients.(1)
Approximately 50% of the patients with aggressive non-Hodgkin's lymphoma (NHL) are above 65 yr of age. The standard treatment of aggressive NHL is CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).(2) Several trials have now been published that studied specifically the clinical effects of CHOP chemotherapy in elderly patients.(3-5) The most important adverse effect of CHOP is neutropenia, resulting in infections or neutropenic fever. This could be prevented by administering granulocyte colony-stimulating factor (G-CSF).(6)
In 1994, the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) initiated a randomized multicenter study in elderly patients ($\geq$ 65 yr) with aggressive NHL to compare CHOP with CHOP

plus prophylactic G-CSF. The aim of the prophylactic administration of G-CSF was to achieve maximal (= standard) dose intensity, resulting in an improved response rate and/or survival. The clinical results of CHOP treatment in the elderly have been published.(7) Although the relative dose intensity of doxorubicin and cyclophosphamide were higher with G-CSF prophylaxis, no improvement of response and survival could be demonstrated.
In this study we prospectively analyzed the changes in QoL during and following treatment.

Patients and Methods

Patients $\geq$ 65 yr of age with a newly diagnosed aggressive NHL with stage II, III or IV disease and a left ventricular ejection fraction $\geq$ 45% were randomized to receive CHOP q 3 wk (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (max 2 mg) intravenously on day 1 and prednisone 50 mg/m^2 orally on days 1-5) or CHOP q 3 weeks combined with filgrastim (Neupogen, Amgen, Thousand Oaks, CA, USA) 300 μg on days 2-11 subcutaneously. The instructions for postponement or dose reduction of chemotherapy have been described earlier.(7)
Complete remission (CR) was defined as disappearance of all symptoms and signs, disappearance of all measurable lesions, normal lactate dehydrogenase (LDH) for at least 6 wk and no bone marrow infiltration. Patients with small (< 1 cm) lymph nodes still present at the end of treatment that showed no progression after 4 months were also considered as CR. Partial response (PR) was defined as a reduction of all measurable lesions with more than 50% and no new lesions. Stable disease (SD) was defined as not fulfilling the PR criteria and no signs of progression. Progressive disease (PD) was defined as the occurrence of a new lesion, or increase of the original tumor mass by more than 25%.
Between August 1994 and September 2000 411 patients from 56 hospitals were enrolled in the clinical study.(7) All patients gave informed consent for study participation according to the regulations of the Dutch Health authorities. The study was performed and evaluated by the independent Dutch-Belgian HOVON group according to the Helsinki agreement.
The Dutch national Health Council financially supported the QoL study for a period of 3 yr. Recruitment started in October 1996 and was closed in June 1999. The physicians asked all patients who were enrolled in the clinical study during this period if they also agreed to participate in the QoL study. If so, consent was asked to send the questionnaires directly to the patients' home address.

Questionnaires

The questionnaire consisted of the EuroQol–5D, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (version 2.0) and the Multidimensional Fatigue Inventory (MFI-20).(8-12)

The EuroQol-5D is a generic instrument, which measures 5 dimensions of health: mobility, self-care, daily activities, pain and anxiety. In the descriptive part the patient is required to rate his or her health on each of the five dimensions by checking one of the three levels of severity: no problems, some/moderate problems or severe problems. The EuroQol-5D index assigns a preference value (utility) to each health state generated by the descriptive part of the questionnaire. A higher value represents a better QoL. The utilities can be used to calculate quality adjusted life years (QALYs).

The EORTC QLQ-C30 is a cancer specific questionnaire, which measures five functional scales, three symptom scales, a global health status scale and five single items. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales implies a better QoL, whereas for symptoms a higher score refers to more symptomatology. The EORTC developed several additional disease specific modules, but a module for NHL was not yet available. So, we added 12 questions specific for NHL or its treatment (Table 1). These additional questions are based on clinical experience and tested for relevance in a small number of patients, but are not extensively validated.

Table 1: **Additional questions concerning NHL and treatment related symptoms**

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
1.	Did you have night sweats?	1	2	3	4
2.	Have you lost weight?	1	2	3	4
3.	Have you had bleeding from nose or gums?	1	2	3	4
4.	Have you had hair loss?	1	2	3	4
5.	Did you have itching?	1	2	3	4
6.	Have you had a skin lesion?	1	2	3	4
7.	Have you had pain in the muscles?	1	2	3	4
8.	Have you had pain in bones or joints?	1	2	3	4
9.	Have you had an infective disease (such as flu, pneumonia, inflammation of the bladder etc.)	1	2	3	4
10.	Have you had palpitations?	1	2	3	4
11.	Have you had tingling hands or feet?	1	2	3	4
12.	Have you had dead fingers or toes?	1	2	3	4

The MFI-20 is a 20-item self-report instrument designed to measure fatigue. It covers the following five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. The instrument consists of 20 statements for which the patient has to indicate on a five-point scale to what extent the particular statement applies to him or her. The endpoints of the scale are “yes, that is true” and “no, that is not true”. All statements refer to aspects of fatigue experienced during the previous days. The total score for all five subscales ranges from 4 to 20, where higher scores indicate a higher degree of fatigue.

The questionnaire was sent to the participating patients before the start of chemotherapy, at 2 wk after the second, fourth and sixth CHOP cycles, and at 3, 6, 10 and 18 months after the last cycle of chemotherapy. The timeframe of 2 wk after a chemotherapy course was chosen because complications related to myelosuppression, such as infections, were expected to occur primarily during the second week following chemotherapy. The time points of QoL evaluation during follow-up were linked to clinical evaluations. In the follow-up period it was checked if the patient was still alive before sending the questionnaire. If a questionnaire had not been returned within 2 wk a reminder was sent. Patients who did not wish to continue participation in the study were asked to return the questionnaire empty.

Analyses

Only patients included in the clinical study between October 1996 and June 1999 were asked to participate in the QoL study. Therefore, the patients in the QoL study were a subgroup of the complete clinical study population. To check if the participating patients were representative for the complete study population several characteristics that are possibly related to QoL were compared between participating patients and all patients in the study by using Pearson’s chi-squared test in case of discrete variables, or the Wilcoxon rank-sum test in case of continuous variables. These items included age, sex, stage of disease, the presence of B-symptoms, elevated LDH, World Health Organization (WHO) performance status, response on protocol treatment and the age-adjusted International Prognostic Index (aaPI).(13)

Based on clinical experience, we assumed that there would be differences in QoL baseline scores between patients with more or less advanced disease. Indeed, baseline scores were highly correlated with aaPI. Therefore, we decided to analyze the results of this QoL study for two separate groups: the group with a low or a low-intermediate aaPI (referred to as low IPI) and the group of patients with a high-intermediate or a high aaPI (referred to as high IPI). The aaPI is determined by three risk factors: (1) Ann Arbor stage 3 and 4, (2) WHO performance status 2 to 4 and (3) LDH $>$ 1 x upper limit of normal.(13) With none of these risk factors the aaPI is low, with one risk factor it is low-intermediate, with two risk factors it is high-intermediate and with three risk factors the aaPI is high.

To evaluate the changes in QoL over time, the mean differences compared to baseline values for a pre-selected number of QoL dimensions were calculated for each of the three measurements during CHOP therapy and for each of the four measurements after completion of treatment.
We hypothesized that the QoL during follow-up would mostly be influenced by disease status, i.e. complete remission, partial remission or no response, and the eventual relapse or progression. So, the QoL of patients with progression during treatment, with relapse after a complete remission or with disease progression after a partial remission, was analyzed separately from the QoL of patients who remained progression-free. Because second-line therapy at the time of relapse/progression differed from no anti-lymphoma therapy to intensive chemotherapy and response to second-line treatment also varied, it was decided to use only the first questionnaire after PD was diagnosed and to omit later questionnaires from the analyses. The completion scheme for questionnaires was based on the date of the last CHOP course rather than on changes in disease status. Consequently, the time between the evidence of relapse or progression and the completion of the QoL questionnaire varied among patients. For all patients with PD, it was checked whether they possibly achieved a CR or PR on second-line treatment at the time of completion of the questionnaire. If so, the questionnaire was omitted from the analyses.
Analyses were based on mean difference scores compared to baseline scores, so all patients who failed to complete the baseline questionnaire had to be omitted from the base-case analysis. The potential influence of missing questionnaires was investigated in a sensitivity analysis, by repeating all analyses using only questionnaires of patients who completed all questionnaires during the study.
In accordance with the literature a difference of $\geq$ 10 points in the EORTC QLQ-C30 was considered to be clinically meaningful.(14-16) Smaller differences were considered to be clinically irrelevant and therefore not statistically tested. Differences of more than 10 points compared to baseline values were tested by using the paired t-test and differences between groups were tested by using the Student's t-test. All reported P-values are two-sided. $P < .01$ are considered to be statistically significant.

Results

Patient Characteristics

In the study period 162 patients from 41 hospitals were asked to participate in the QoL study, of whom 30 patients refused. The participating patients differed from the complete clinical study population in having less B-symptoms (26% vs. 36%, $P < .01$) and in a lower proportion of patients having an elevated LDH (51% vs. 61%, $P < .01$). Four patients who completed only one questionnaire were omitted from all analyses. The patient characteristics of all eligible patients in the clinical study (n = 389) and of the 128 patients who participated in the QoL study are shown in Table 2.

Table 2: **Patient characteristics in the QoL study and in the clinical study**

		QoL study	Clinical study
Total		128	389
Sex			
	Male	56%	56%
	Female	44%	44%
Age, years			
	Mean	72	73
	Median	72	72
	Range	65-84	65-90
WHO performance status			
	0 – 1	84%	81%
	2 – 4	16%	19%
Ann Arbor stage			
	II	27%	25%
	III	17%	20%
	IV	56%	55%
B-symptoms present		26%*	36%
LDH elevated		51%*	61%
Age-adjusted IPI			
	Low	15%	11%
	Low-intermediate	38%	34%
	High-intermediate	38%	43%
	High	9%	12%
CR on protocol		56%	53%

* $p < .01$

Abbreviations: QoL, quality of life; WHO, World Health Organization; LDH, lactate dehydrogenase; IPI, International Prognostic Index; CR, complete remission.

Response to Questionnaires

Of the 128 participants, 97 patients completed all questionnaires during treatment and 52 patients completed all eight questionnaires. Twelve patients failed to complete the baseline questionnaire because of logistic problems. Sixteen patients missed one questionnaire during therapy or follow-up, and 18 missed two.

In total, 801 questionnaires (92%) were returned. The overall return rate during treatment was 96%, while during follow-up the overall return rate was 88%. 11 patients discontinued their participation early by returning a questionnaire empty. Detailed return rates are shown Table 3. There were no differences in return rates between the groups low IPI and high IPI.

Table 3: **Compliance with completion of questionnaires**

Form	Baseline	Cycle 2	Cycle 4	Cycle 6	3 months	6 months	10 months	18 months
Expected*	132	130	119	111	PF: 99 PD: 15	PF: 83 PD: 20	PF: 69 PD: 20	PF: 56 PD: 14
Completed	119	128	116	107	PF: 91 PD: 11	PF: 76 PD: 15	PF: 60 PD: 16	PF: 51 PD: 11
Return rate (%)	90.1	98.5	97.5	96.4	PF: 91.9 PD: 73.3	PF: 91.6 PD: 75.0	PF: 87.0 PD: 80.0	PF: 91.0 PD: 78.6

* The expected number during treatment (after cycle 2, 4, 6) is defined as the total number of patients alive and on treatment. The expected number during follow-up is defined as the number of patients alive and classified according to disease status.
PF = progression-free, PD = progressive disease.

QoL during CHOP Treatment

No significant differences in QoL were observed by the addition of G-CSF to standard CHOP chemotherapy. Therefore the results could be analyzed without taking into account the treatment arm of the clinical study.

The aaPI was strongly correlated to most of the baseline QoL values (see Table 4). Patients with a low or low-intermediate aaPI had a significant better quality of life than patients with a high-intermediate or high aaPI on almost all dimensions.

Table 4: **Baseline mean (median) scores for pre-selected variables.**

	Age-adjusted IPI 0-1	Age-adjusted IPI 2-3	P
Number of patients	63	53	
EuroQol index	0.74 (0.80)	0.44 (0.49)	.000
QLQ-C30			
Physical function	65 (60)	45 (40)	.000
Role function	63 (67)	40 (33)	.000
Emotional function	75 (75)	67 (67)	.060
Cognitive function	85 (100)	72 (83)	.008
Social function	80 (83)	64 (67)	.006
Global QoL	65 (67)	48 (50)	.000
Fatigue	33 (33)	58 (56)	.000
Pain	20 (20)	37 (33)	.007
Sleeping difficulty	35 (33)	38 (33)	.723
Appetite loss	20 (0)	36 (33)	.014
NHL specific symptoms			
Night sweats	25 (0)	33 (33)	.244
Weight loss	25 (0)	47 (33)	.001
CHOP specific symptom			
Peripheral neuropathy	5 (0)	9 (0)	.141
MFI-20			
General fatigue	12 (12)	16 (17)	.000
Physical fatigue	12 (12)	16 (16)	.000
Reduced activity	14 (15)	17 (19)	.002
Reduced motivation	12 (12)	14 (15)	.026
Mental fatigue	9 (8)	11 (11)	.019

A higher score on EuroQol and EORTC QLQ-C30 function scales implies a better QoL, whereas for symptoms a higher score refers to more symptoms.

Higher scores on MFI-20 indicate a higher degree of fatigue.

Table 5: **Mean change scores of EuroQol and EORTC QLQ-C30 during 1st line CHOP treatment compared to baseline scores, according to age-adjusted IPI (aaPI) score.**

	After 2nd CHOP cycle		**After 4th CHOP cycle**		**After 6th CHOP cycle**	
	aaPI 0-1	aaPI 2-3	aaPI 0-1	aaPI 2-3	aaPI 0-1	aaPI 2-3
Number of patients	63	52	57	48	54	44
EuroQol index	- 0.03	+ 0.07	- 0.02	+ 0.15	- 0.05	+ 0.09
Physical function	-4	- 1	- 7	+ 2	-14*	+ 1
Role function	-2	+ 3	- 6	+ 7	-17*	+ 6
Emotional function	+ 10*	+ 10*	+ 10*	+ 8	+ 9	+ 9
Cognitive function	+ 2	+ 5	+ 1	+ 1	- 1	+ 3
Social function	- 2	+ 1	- 1	+ 2	- 8	- 3
Global QoL	- 2	+ 9	- 8	+ 4	- 14*	+ 7
Fatigue	+ 13*	- 6	+ 18*	- 3	+ 24*	- 2
Pain	- 5	- 10	- 7	- 19*	+ 2	- 14
Sleeping difficulty	- 6	- 7	- 4	- 5	- 3	- 14*
Appetite loss	+ 1	- 5	+ 8	- 8	+ 8	- 8
Night sweats	- 12*	- 18*	- 12	- 12	- 7	- 19*
Weight loss	- 4	- 14*	- 10	- 32*	- 3	- 31*
Peripheral neuropathy	+ 8	+ 15*	+ 20*	+ 21*	+ 20*	+ 25*

* $P < .01$

Note: a positive score for EuroQol, functional dimensions and global QoL implies an improvement, whereas a positive score on the symptom scales implies more symptoms.

During treatment the changes in QoL of the patients with a low or low-intermediate aaPI differed from changes in QoL in the patients with a high-intermediate or high aaPI. After the sixth CHOP cycle, a significant decline in physical function, role function and in global QoL was observed in the low IPI group, whereas functioning remained stable in the high IPI group (Table 5). Fatigue increased significantly during treatment only in the low IPI group (Fig. 1). No additional value of the MFI-20 over the fatigue subscale of the QLQ-C30 could be demonstrated in this patient group. Differences in the MFI-20 were also found in the QLQ-C30. General fatigue, physical fatigue and reduction in activity of the MFI-20 showed the same pattern. Mental fatigue was more or less comparable to emotional functioning of the QLQ-C30. Soon after the start of treatment, in both groups emotional function improved and night sweats decreased. Two questions concerning peripheral neuropathy were added because we expected a considerable change during and following treatment. Peripheral neuropathy, a side effect of vincristine, increased in both low and high IPI groups. All change scores compared to baseline for pre-selected variables are shown in Table 5.

QoL during Follow-up

No significant differences in QoL were observed between patients who reached a CR and patients who reached a PR. Patients in complete remission and patients with a stable partial remission therefore were combined into the group “progression-free”.

The improvement of emotional functioning during CHOP chemotherapy continued during follow-up in patients who remained progression-free.

In the progression-free patients the increased fatigue in low IPI patients returned to baseline values during follow-up, whereas fatigue in high IPI patients declined significantly as compared to baseline. (Fig. 1) The same pattern was seen for physical function and role function. Social functioning and complaints of sleeping difficulty improved in both groups and complaints of appetite loss improved in the high IPI group. If complaints of peripheral neuropathy had developed during CHOP therapy they remained present up till 18 months after completion of therapy.

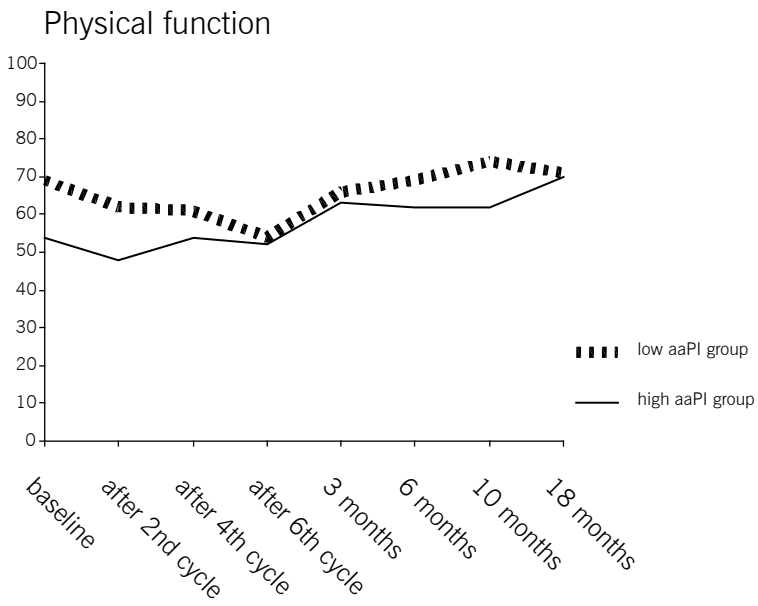
At the time of disease relapse or progression, QoL was comparable to baseline in the high IPI group and worse compared to baseline in the low IPI group. Some change-scores do not reach statistical significance, since the number of observations was only 13.

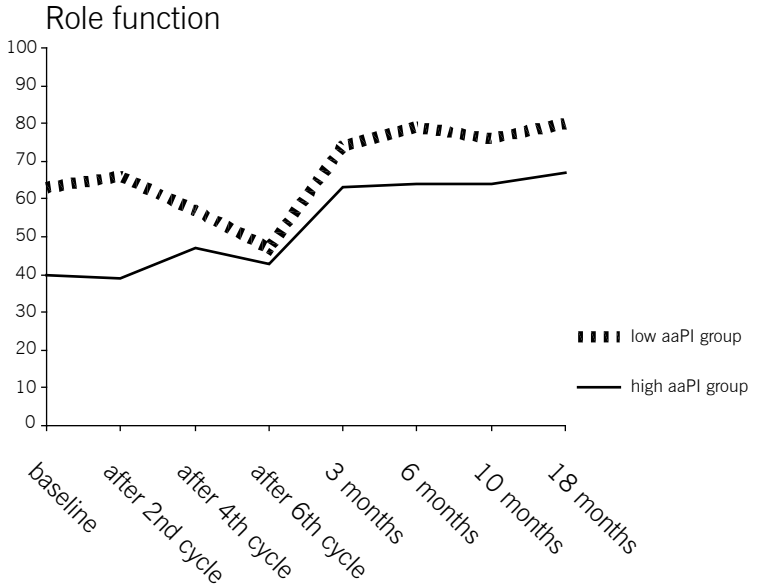
All change-scores of pre-selected variables during follow-up are shown in Table 6. From Tables 5 and 6 it can be read that the number of patients that could be included in the analyses decreased from 63 to 26 in the low IPI group and from 52 to 20 in the high IPI group. This decrease in patient numbers implies a decrease in statistical power. This reduces the likeliness of statistical significance, even for relatively large differences in change scores.

Sensitivity Analysis

Repeating all analyses with the patients who completed all questionnaires did not change the results.

Fig 1: **Changes in quality of life (EORTC QLQ-C30) during treatment and in follow-up for patients remaining progression-free with low/low intermediate (n = 26) or high intermediate/high aaPI (n = 20)**




Role function
100
90
80
70
60
50
40
30
20
10
0
low aaPI group
high aaPI group
baseline
after 2nd cycle
after 4th cycle
after 6th cycle
3 months
6 months
10 months
18 months

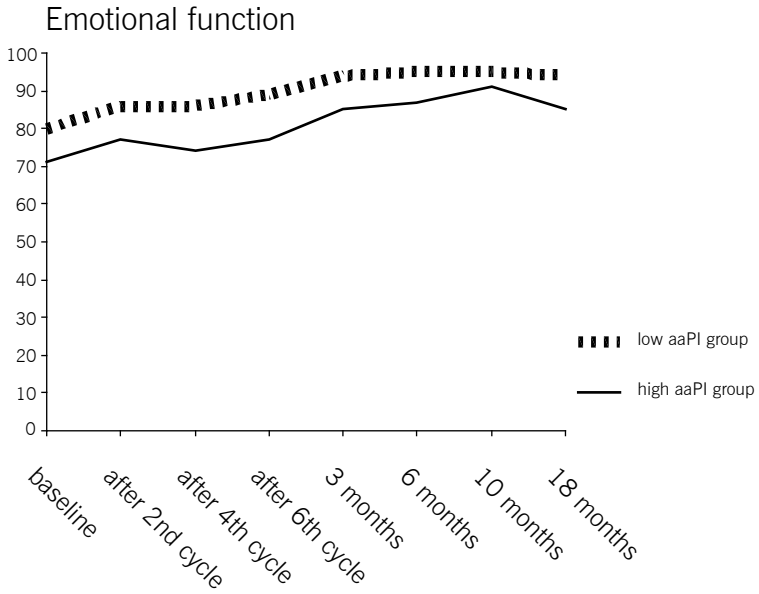

Emotional function
100
90
80
70
60
50
40
30
20
10
0
low aaPI group
high aaPI group
baseline
after 2nd cycle
after 4th cycle
after 6th cycle
3 months
6 months
10 months
18 months

Fig 1: **Changes in quality of life (EORTC QLQ-C30) during treatment and in follow-up for patients remaining progression-free with low/low intermediate (n = 26) or high intermediate/high aaPI (n = 20)**

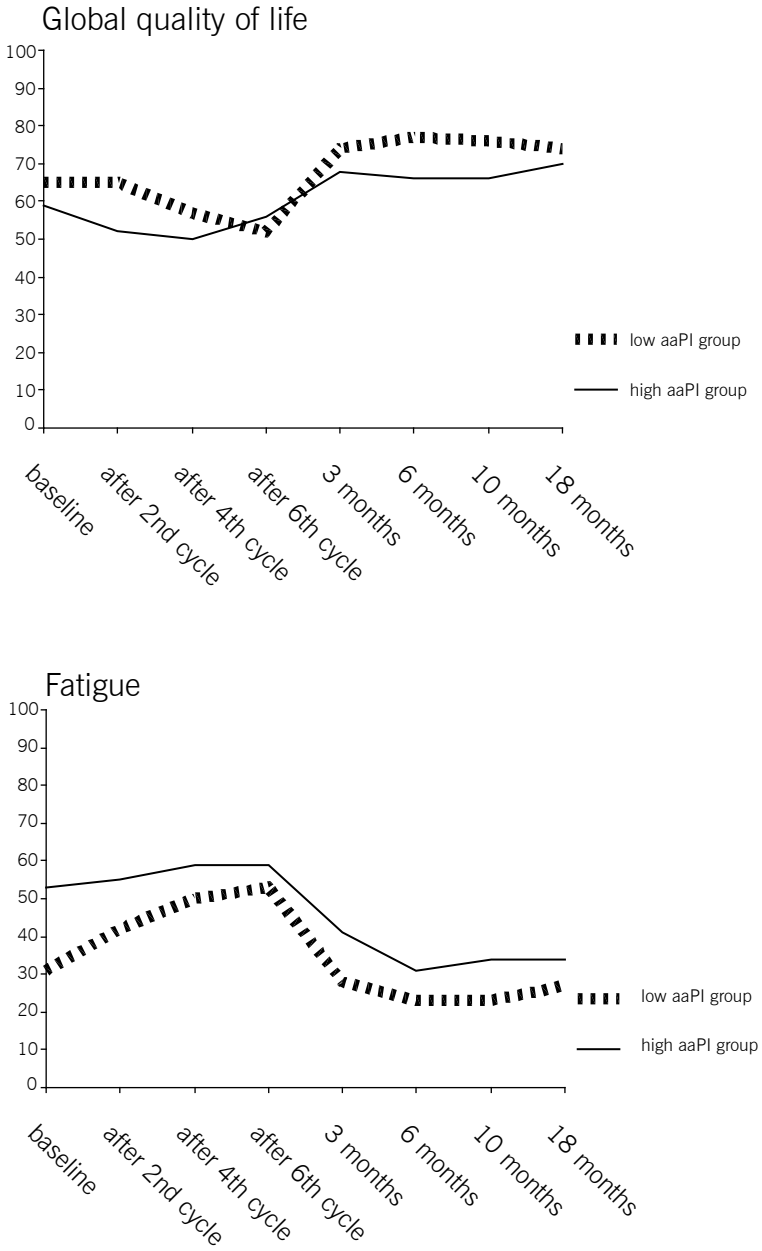


Table 6: **Mean change scores of EuroQol and EORTC QLQ-C30 during follow-up compared to baseline scores according to age-adjusted IPI score.**

	Progression-free at 3 months		**Progression-free at 6 months**		**Progression-free at 10 months**		**Progression-free at 18 months**		**At progression**	
	aaPI 0-1	aaPI 2-3	aaPI 0-1	aaPI 2-3	aaPI 0-1	aaPI 2-3	aaPI 0-1	aaPI 2-3	aaPI 0-1	aaPI 2-3
Number of patients	44	39	41	27	31	23	26	20	13	13
EuroQol index	+ .07	+ .23*	+ .07	+ .17	+ .04	+ .14	+ .06	+ .14	- .24	- .04
Physical function	- 1	+ 11	- 2	+ 9	+ 4	+ 9	+ 1	+ 15	- 27	- 2
Role function	+ 8	+ 17	+ 13	+ 18	+ 11	+ 17	+ 13	+ 17	- 23	- 3
Emotional function	+ 14*	+ 16*	+ 12*	+ 15*	+ 14*	+ 15*	+ 14*	+ 13*	- 2	- 3
Cognitive function	+ 1	+ 9	+ 1	+ 3	0	+ 12	+ 1	+ 8	- 10	- 3
Social function	+ 9	+ 9	+ 9	+ 11	+ 13	+ 14	+ 16*	+ 12	- 15	- 5
Global QoL	+ 7	+ 16*	+ 7	+ 13	+ 7	+ 9	+ 8	+ 10	- 18	0
Fatigue	- 1	- 14	+ 1	- 18*	- 1	- 22*	0	- 18*	+ 24	- 6
Pain	- 6	- 18*	- 7	- 13	- 2	- 12	- 1	- 13	+ 3	- 1
Sleeping difficulty	- 10	- 10	- 13	- 10	- 18*	- 23*	- 19*	- 20*	- 3	+ 5
Appetite loss	- 3	- 27*	- 3	- 22*	- 5	- 20*	- 5	- 20*	+ 18	- 10
Night sweats	- 19*	- 22*	- 19*	- 27*	- 15	- 26*	- 15	- 28*	+ 6	- 3
Weight loss	- 16*	- 32*	- 17	- 36*	- 18	- 36*	- 26*	- 35*	+ 6	- 22
Peripheral neuropathy	+ 19*	+ 25*	+ 15*	+ 28*	+ 13*	+ 25*	+ 15*	+ 15*	+ 17	+ 30

* $p < .01$

Discussion

The main purposes of this QoL study were to describe the development of patients' QoL during and following CHOP chemotherapy and to compare QoL between patients who did or did not receive prophylactic G-CSF during CHOP. The clinical study showed no beneficial effects of the prophylactic use of G-CSF on response rate or survival.(7) In addition, prophylactic G-CSF added to CHOP in these elderly patients did also not improve the QoL. Therefore, we emphasized on the changes of patients' QoL irrespective of the treatment arm in the clinical study.

Representativeness of the Study Group

The validity of QoL studies depends on the proportion of participating patients and the percentage of returned questionnaires among participants. Problems may arise when positive or negative selection occurs. Non-participants in QoL studies are usually older and/or have more symptoms.(17) In this study designed for elderly patients the participation was high, namely 81% of the patients that were asked to participate. Comparing the clinical data of participants and non-participants a difference in presence of B-symptoms and elevated LDH was observed, B-symptoms and elevated LDH being more frequent in the non-participants. The presence of B-symptoms was inversely correlated with QoL before and during early treatment (data not shown). Elevated LDH is one of the determinants of the aaPI, and almost all patients in the higher aaPI group had an elevated LDH. During the follow-up the non-response was higher among patients with progression or relapse. Assuming that the patients with most complaints stopped returning the questionnaires the QoL scores of progression or relapse would be overestimated.

Questionnaires

The results of the MFI-20 questionnaire yielded no additional information compared to the EORTC QLQ-C30 fatigue and emotional function scales. In future QoL studies a special fatigue questionnaire in addition to the EORTC QLQ-C30 questionnaire seems unnecessary in this patient group, unless fatigue itself is the specific subject of research.

Quality of Life in the Elderly Patients

This QoL study showed that standard CHOP-chemotherapy was tolerated well by elderly patients, as long as they were fit enough to be included in a clinical trial with standard inclusion and exclusion criteria. The Nordic Lymphoma Group recently used the QLQ-C30 in a randomized trial of CHOP versus MACOP-B in patients with lymphoma. In that study the median age was 46 yr, and the upper age limit was 66 yr. The mean QoL scores 1 yr after therapy were not clearly different from the reference population.(18) We had no QoL data on a Dutch elderly reference population, but our results do not suggest an important long-term effect on QoL. The overall pattern in this QoL analysis was that patients with a low or low-intermediate aaPI, representing less aggressive disease, had a better QoL at baseline compared to patients with aggressive disease as represented by a high-intermediate or high aaPI. In the former patient group, functioning deteriorated and fatigue increased during CHOP chemotherapy (to the same level where patients with a high-intermediate or high IPI started before treatment), whereas functioning and the level of fatigue remained stable for the latter patient group. During progression-free follow-up, QoL returned to at least baseline values in the low IPI group and improved considerably compared to baseline values in the high IPI group. However, progression-free patients with a high IPI at diagnosis never reach the absolute values of the progression-free low IPI patients. Patients with disease progression had the worst QoL. So, in these elderly patients the QoL was determined by two factors, i.e. aggressiveness of disease and toxicity of treatment. In the case of aggressive disease the QoL was reduced at presentation but improved by CHOP, because the effects of disease were more important than the toxicity of treatment. With less aggressive disease the QoL was better at presentation, but declined during therapy because now toxicity was more important. At the end of treatment QoL returned to pretreatment levels. In future studies these two factors should be analyzed separately.

New Development in Lymphoma Treatment

Recently, management of diffuse large B-cell lymphomas in elderly patients has changed with the addition of new modalities (rituximab) or intensification (2-weekly CHOP plus G-CSF).(4, 19) The changes in toxicity and effectiveness due to these new approaches might also result in different QoL patterns.

This large prospective multicenter study included many patients from both university and community hospitals, and was a representative sample that reflected the clinical practice in the Netherlands. We conclude that the results of this QoL analysis could be useful and relevant in discussing the effects of CHOP-treatment with patients. Especially in the counseling of patients with a higher aaPI, who generally have more symptoms and a reduced QoL at diagnosis, this study showed that the QoL did not deteriorate further due to the chemotherapy, and improved at the end of treatment.

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ECONOMIC EVALUATION OF PROPHYLACTIC GRANULOCYTE COLONY STIMULATING FACTOR DURING CHEMOTHERAPY IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA.

Chapter 5

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Abstract

Background and objectives: Treatment with CHOP chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma (NHL) is less effective and accompanied by more adverse effects than in younger patients. The prophylactic use of granulocyte colony-stimulating factor (G-CSF) might improve the results, but increases the costs of treatment. We analyzed the costs of therapy and follow-up of patients with NHL treated with CHOP with or without G-CSF prophylaxis.
Design and methods: Four hundred and eleven patients were randomized for treatment with CHOP or CHOP plus G-CSF. A detailed study of treatment costs from randomization until 3 years of follow-up or death was performed in a subset of 100 out of 389 eligible patients. Because costs during follow-up were independent of the use of G-CSF during treatment, costs of follow-up and second-line treatment were calculated irrespective of the treatment arm.
Results: Total hospital costs for first-line treatment were € 12,178 [95% CI € 10,297 – € 14,059] for CHOP alone and € 18,356 [95% CI € 15,807 – € 20,906] for CHOP plus G-CSF. Costs during follow-up showed a wide difference (range € 74 – € 53,925) depending on disease status and choice of treatment in case of relapse or progression.
Interpretation and conclusions: The clinical study showed no difference between the treatment arms in response, overall survival or event free survival, while the costs were significantly higher in the G-CSF arm. We conclude that the addition of prophylactic G-CSF to CHOP chemotherapy is not cost-effective in these patients.

Introduction

Non-Hodgkin's lymphoma (NHL) is the most common hematological malignancy in adults. Its incidence shows a steady increase of 4% per year, both in the USA and Europe.(1, 2) The incidence increases with age. Standard first-line therapy for aggressive (diffuse large B-cell, peripheral T-cell lymphoma), disseminated NHL has been CHOP chemotherapy ever since the mid-1970's.(3-5) However, for a long time, this regimen has been considered too toxic for elderly patients.(6, 7) Therefore, several chemotherapy regimens were developed to reduce toxicity, but none of these turned out to be as effective as CHOP.(8-12) Presently 50% of elderly patients will obtain a complete remission, although only half of them will be cured.(10-13) Higher age has shown to be a negative prognostic factor for both complete remission and survival.(14) One possible reason for the poor outcome is that elderly patients tolerate combination chemotherapy less well than younger patients do. Elderly patients more often develop leucopenia and as a result

infectious complications. Leucopenia often results in postponement of chemotherapy courses and/or dose reduction. This leads to a lower relative dose intensity, which might negatively affect cure rates.(15)

Hematopoietic growth factors, such as recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) and recombinant human granulocyte colony-stimulating factor (rhG-CSF) shorten the duration of neutropenia.(13, 16-18) Thus, they have the potential to reduce costs for antibiotics and hospitalization. Furthermore, the cost of prophylactic G-CSF use may be justified if it is compensated for by objective clinical benefits or by a subjectively perceived improvement of the quality of life. The high incidence of neutropenia and its consequences (infections) are more evident in elderly patients, so these patients might particularly benefit from prophylaxis with growth factors. On the other hand, as the incidence of NHL rises with 4% per year, routine G-CSF use in these patients might result in substantial increases in health care expenses.

In the Netherlands, a large randomized clinical trial was organized in order to study whether the effect of primary G-CSF prophylaxis in addition to standard CHOP chemotherapy in elderly patients with aggressive NHL would improve the treatment outcome.(19) G-CSF improved the relative dose intensity of CHOP, but this did not lead to a higher complete response rate or better overall survival. Another major goal was to evaluate the cost-effectiveness of this approach. This paper presents the results of the cost analysis.

Design and Methods

Patients ≥ 65 years with a newly diagnosed intermediate or high grade NHL according to the Working Formulation, stage II, III or IV according to the Ann-Arbor classification were randomized to receive either 6-8 CHOP cycles (cyclophosphamide 750 mg/m2 iv, day 1; doxorubicin 50 mg/m2 iv, day 1; vincristine 1.4 mg/m2 (maximum 2 mg) iv, day 1; prednisone 50 mg/m2 orally, days 1-5) q 3 weeks or the same chemotherapy plus prophylactic G-CSF (filgrastim, Amgen, Thousand Oaks, CA), 300 μg sc daily, days 2-11. The study was initiated and independently conducted by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and was open to community and university hospitals in The Netherlands and Belgium.

Primary endpoints of the trial were complete remission (CR), overall survival (OS), event-free survival (EFS), progression-free survival (PFS) from randomization and disease free survival (DFS) from CR. Secondary endpoints were the relative dose intensity of CHOP, the incidence and severity of infections, the number of days with fever, use of antibiotics, quality of life evaluation and health economic aspects.

For the cost analysis, total costs from a societal perspective were calculated from the date of randomization until the completion of 3 years of follow-up or death, whichever occurred first.(20) A societal perspective implies that all costs resulting from a medical intervention to society are taken into account, instead of only calculating the costs of the medical intervention itself.(20) Because patients were at least 65 years of age and therefore retired, it was not necessary to take into account costs due to productivity losses (due to absence from work) as required by the study perspective.

For the calculation of costs generated in the hospital, a subset of 100 Dutch patients was selected out of the 389 patients of the total clinical trial population (50 patients in each treatment group). From the first randomized patient in 1994 onwards, the first 100 patients were selected based on the following criteria: within each hospital patients from both trial arms, patients from both university hospitals and community hospitals, and a minimum time of 2.5 years from randomization until the planned date of the cost analysis. The first and the second selection criterion were chosen to compensate for possible cost differences caused by local hospital variables. The third criterion was necessary to ensure that most patients would have complete data at the time of the analysis. Individual hospital records of the selected patients were studied in detail to determine inpatient and outpatient resource utilization. Costs for hospitalization or interventions that were not related to NHL were excluded from analysis.

Data on a) visits to the general practitioner, b) cost of patient traveling, c) the consumption of informal care, d) community nurse help and e) home assistance were collected by questionnaires. One hundred and thirty-two patients from the total study group participated in a quality of life study. Questions about the use of outpatient resources were added to the forms of the quality of life study. They were sent to the patients' home address before start of treatment, after the 2nd, 4th and 6th cycle of chemotherapy and 3, 6, 10 and 18 months after completion of treatment. The period of resource use mentioned in the questionnaire (the last week or the last month) was considered representative for the whole period between two questionnaires.

Total costs were calculated by multiplying the units of resource utilization by the cost per unit. For the most important items within the resource utilization, unit costs were calculated on the basis of financial data from 2 university hospitals and 2 community hospitals, reflecting full hospital costs, including overhead costs.(21, 22) The micro-costing method was used for the calculation of these unit costs. This method relies on a detailed inventory and measurement of resources consumed.(23) Finally, unit costs were weighted for the type of hospital from which they originated in the clinical study (i.e. 30% university and 70% community hospital). The weighted unit cost of an inpatient day applied in this study was € 328 (57% personnel costs (P), 14% material costs (M) and 29% overhead costs (O)). The unit cost of a day-care treatment was € 128 (44% P, 18% M and 38% O) and for an outpatient visit was € 58 (80% P, 4% M and 16% O). Diagnostic tests and other procedures were multiplied by Dutch charges, as these are proper approximations of the actual unit costs.(24) Costs of medication were based on Dutch wholesale

prices.(25) The original base year was 1997 and costs were indexed to 2002 prices using price indices as provided by Statistics Netherlands (www.cbs.nl). Total costs were divided into costs of first-line treatment and costs of follow-up. In economics it is assumed that individuals prefer good outcomes to occur sooner rather than later. Thus, to correct for the passage of time, outcomes are discounted, generally at a constant rate. For costs in the 2nd and 3rd year a recommended discount rate of 4% was applied.(22) Because no relation was assumed between the use of G-CSF during first-line treatment and cost during follow-up, this were calculated irrespective of treatment arm and attributed to the treatment outcome.

Statistics

Statistical analysis was performed by using SPSS for Windows, version 10.0. Because cost data generally do not have a normal distribution, as a first approach the non-parametric Mann-Whitney U-test was applied, using a two-sided significance level $\alpha = 0.05$. Secondly, costs were additionally compared by the non-parametric "bootstrap test", as recommended, given its independence from the sample size distribution.(26) The bootstrap test is a way of estimating a parameter's distribution by means of a large number of simulations, based on 'drawing with replacement' from the original data. To obtain this, 4 steps are undertaken: 1. Draw with replacement N_A pairs of costs and effects from patients in group A (N_A representing the number of patients in group A), 2. Calculate mean costs (and effects) from this new sample, 3. Repeat these steps for group B, 4. Calculate the difference in mean costs (and effects) between the result of step 2 for group A and the result of step 2 for group B (and, if desired, the incremental cost-effectiveness ratio by dividing the cost difference by the difference in effects). These 4 steps represent 1 bootstrap simulation. In total, 1000 simulations were executed. On the basis of these simulations, a confidence interval was calculated using the so called 'percentile method', implying that the results of the 1000 simulations were consecutively ordered and the borders of the 95% confidence interval were indicated by the 25^{th} and 975^{th} observation.(26-29).

All data are presented as mean values per patient. Significance levels shown in the tables result from the Mann-Whitney U-test. The confidence intervals resulting from the bootstrap test are only shown if the result differs from the Mann-Whitney U-test.

Results

Main Results of the Clinical Trial

From August 1994 until September 2000, 411 patients were enrolled in the clinical study and 389 of them were eligible for evaluation: 192 patients were randomized to CHOP and 197 patients to CHOP plus G-CSF. The relative dose intensity of cyclophosphamide (median 93.9% vs 96.3%, P = .01) and doxorubicin (median 93.3% vs 95.4%, P = .04) was significantly higher in the CHOP plus G-CSF group and the median duration of antibiotic use was 0 as compared to 6 days in the CHOP group. However, no differences were observed between the treatment groups with respect to overall response or survival. Also, no differences in quality of life could be demonstrated. The patients' characteristics and main outcomes are presented in Table 1. The clinical results have been reported in detail elsewhere.(19)

Table 1: **Main outcomes of the clinical study**

	CHOP n = 192	**CHOP + G-CSF n = 197**	**P value**
Complete response rate	55%	52%	.63
Overall response rate	83%	85%	.70
Overall survival at 5 years	22%	24%	.76
Event-free survival at 5 years	18%	17%	.52
Progression-free survival at 5 years	24%	25%	.65
Disease-free survival at 5 years	43%	40%	.31
Infection WHO grade 3-4 *	3%	3%	.82
Infection WHO grade 2-4 *	15%	11%	.007
Patients experiencing fever	45%	37%	
Median duration of fever in patients with fever, in days (mean)	3 (4.7)	2 (3.0)	
Median days with fever, all patients (mean)	0 (2.1)	0 (1.1)	.056
Median days on antibiotics (mean)	6 (16)	0 (8)	.006

* : Calculated per total number of chemotherapy cycles, i.e. 1195 (CHOP) and 1191 (CHOP + G-CSF)

Representativeness of Patients in the Cost Analysis

One hundred patients were selected for the cost analysis study regardless of and without information on their disease status or treatment outcome. Apart from the costs of first-line treatment, the total costs of the three-year study period were expected to be mainly determined by toxicity, disease progression or relapse. The characteristics and the clinical outcome of the 100 patients in the cost analysis were compared with those of the whole clinical study population. No significant differences were observed for any patient characteristic (Table 2). With respect to the clinical outcome, no significant differences were found: 57% of the patients selected for the cost analysis reached a CR. Their overall survival at 1, 2 and 3 years from randomization was 64%, 47% and 39%, respectively. The median survival was 22 months. The event-free survival at 3 years from randomization was 23%. For all 389 patients in the clinical study, the CR rate was 53%, while the overall survival at 1, 2 and 3 years from randomization was 64%, 46% and 37% respectively. The median survival was 21 months and the event-free survival at 3 years from randomization was 26%. In the total study population 30% of the patients were treated in a university hospital, as compared to 44% in the cost study. As mentioned in the "methods" section, a correction for this difference was made in the cost calculation weighting the unit costs for their origin. The results presented below only relate to the 100 patients selected for the cost analysis.

Costs of First-line Treatment

The mean duration of treatment was 163.1 days (CHOP, range 44-365) versus 152.5 days (CHOP plus G-CSF, range 3-287, P = .42). The mean number of CHOP cycles was 6.2 in the CHOP arm (range 2–8) and 5.9 in the CHOP plus G-CSF arm (range 1–8) The median number of CHOP cycles was 6 in both treatment groups. Three out of 50 patients randomized to CHOP alone received G-CSF for an average of 8.3 days (range 1-23). One out of 50 patients randomized to CHOP plus G-CSF never received G-CSF. This patient died on day 2 after randomization. The mean number of days with G-CSF in the remaining 49 patients in the CHOP plus G-CSF group was 57.3 (range 10-88).

Table 2: **Patient characteristics in the entire clinical study and cost study**

	CHOP Cost study	**CHOP Clinical study**	**CHOP + G-CSF Cost study**	**CHOP + G-CSF Clinical study**
No. of patients	50	192	50	197
Age, years				
Mean	74	73	73	73
Median	74	73	73	72
Range	65-89	65-90	65-90	65-90
Sex				
Male	48%	57%	50%	54%
Female	52%	43%	50%	46%
B-symptoms				
Yes	36%	37%	36%	36%
No	64%	63%	64%	64%
WHO performance				
0 – 1	80%	81%	80%	82%
2 - 4	20%	19%	20%	18%
Ann Arbor stage				
II	38%	25% *	22%	25%
III	14%	17%	24%	23%
IV	48%	58%	54%	52%
Age-adjusted IPI				
Low	16%	11%	16%	11%
Low-intermediate	38%	33%	40%	36%
High-intermediate	28%	43% **	32%	43% ***
High	18%	13%	12%	11%

* : P = 0.19

** : P = 0.25

*** : P = 0.51

The total number of hospital days was 15.0 (CHOP, range 0-94) versus 17.2 (CHOP plus G-CSF, range 0-73, P = .56). Reasons for hospitalization were all related to NHL and/or CHOP treatment. In both treatment groups, 30 out of 50 patients (60%) were hospitalized during their first cycle of CHOP. Inpatient treatment for the first CHOP cycle occurred more commonly in community hospitals (77%) than in university hospitals (39%). Because the patients in both treatment arms were equally divided over the community and university hospitals, this did not influence the cost comparisons. Fourteen patients (6 CHOP vs. 8 CHOP plus G-CSF) received radiotherapy during or after completion of chemotherapy. During treatment, 29 patients treated with CHOP received red blood cell transfusions, (mean 5.0 units, median 4) compared to 18 patients treated with CHOP plus G-CSF (mean 5.8, median 4). Platelet transfusions were required in 3 patients in the CHOP arm (mean 3.3 units) and in 2 patients in the CHOP plus G-CSF arm (mean 6.0 units).

Total average hospital costs (in- and outpatient, including medication used at home) for first-line treatment amounted to € 12,178 [95% CI € 10,297 – € 14,059] for patients treated with CHOP and € 18,356 [95% CI € 15,807 – € 20,906] for patients treated with CHOP plus G-CSF.

Data on costs outside the hospital were collected through questionnaires completed by patients who participated in the quality of life study. Response rates to questionnaires during first-line therapy were high: 90% of pre-treatment questionnaires were returned, 98% after the 2nd course, 97% after the 4th course and 96% after the 6th course. Prior to treatment no differences in resource use were present between the two study arms. During treatment, the number of visits to the general practitioner and the use of assistance with housekeeping were comparable in both groups. Patients in the CHOP plus G-CSF arm had significantly more support from a community nurse: 7.2 hours versus 2.5 hours in the CHOP arm (P < .01). Before starting treatment, 97% of patients did not use support from a community nurse. During treatment, 89% of patients in the CHOP arm and 55% in the CHOP plus G-CSF arm did not get home nursing assistance (P=.0001). One third of patients in the CHOP plus G-CSF group needed assistance from a community nurse for the G-CSF injections. Although the amount of informal care was asked about in the questionnaires, it was not possible to translate the obtained information into costs. The patients were not able to estimate the number of hours of informal care exactly. Common answers were: “if needed”, “much”, “sometimes” and “always”. Therefore, informal care is only described without valuing it. Before the start of treatment, 59% of patients received informal care.

Table 3: **Average resource use (median) and corresponding mean costs (median) in Euros during first-line treatment**

	Resource use		Costs in Euro		
	CHOP N = 50	**CHOP+G-CSF N = 50**	**CHOP**	**CHOP + G-CSF**	**P**
Hospital days	15.2 (10)	17.3 (8)	4998 (3606)	5670 (2623)	.73
Day care treatments; chemotherapy	5.2 (6)	4.4 (6)	666 (768)	562 (768)	.14
Day care treatments; transfusion	0.6 (0)	0.4 (0)	83 (0)	47 (0)	.07
Outpatient visits; hematologist	10.44 (10)	9.00 (10)	603 (578)	520 (578)	.25
Outpatient visits; other	1.22 (0)	1.08 (0)	71 (0)	63 (0)	.42
Units of red blood cells	2.9 (2)	2.1 (0)	553 (381)	398 (0)	.04
Units of platelets	0.20 (0)	0.24 (0)	46 (0)	55 (0)	.66
Radiotherapy	6 patients	8 patients	296 (0)	395 (0)	.57
Laboratory tests			841 (741)	768 (606)	.45
Other diagnostic procedures			1351 (1,175)	1260 (1,213)	.67
Chemotherapy			1846 (1,830)	1,755 (1,831)	.54
Antibiotics			420 (161)	197 (10)	< .01
Other medication			292 (279)	322 (279)	.88
Total hospital costs, excl. G-CSF			12,122	1,2052	.49
G-CSF	0.5 (0)	57 (60)	56 (0)	6,304 (6,741)	< .001
Total hospital costs, incl. G-CSF			12,178	18,356	< .001
General practitioner, incl. traveling costs	3.9 (2)	4.1 (2)	73 (37)	77 (37)	.89
Community nurse (hours)	2.5 (0)	7.2 (0)	90 (0)	253 (0)	< .001
Home help (hours)	10.5 (0)	14.8 (0)	207 (0)	290 (0)	.27
Total treatment costs			12,548 (11,726)	18,976 (17,788)	< .001

This percentage remained stable during CHOP courses (64% after 2nd course, 60% after 4th course and 61% after 6th course) and there were no differences between the two treatment arms. All resource use and costs during first-line treatment are shown in Table 3.

Costs of Follow-up

Twelve of the 100 patients died during first-line therapy and consequently had no follow-up costs. The mean duration of the first-line treatment of the 88 patients who remained alive was 5.5 months. The costs of treatment during follow-up were calculated until three years after randomization. Because costs during follow-up were supposed to be mainly dependent on the treatment outcome, these costs were calculated separately for patients who did not experience a relapse or disease progression during the follow-up period (n = 40) and for patients who experienced at least one episode of relapse or disease progression (n = 48). The first group of 40 patients consisted of patients who remained in CR during the 3-year period of the study (n = 23), patients who died in CR (n = 9), patients who remained in PR (n = 4) and patients who died in PR (n = 4). The second group of 48 patients consisted of patients who had progressive disease immediately after treatment (n = 16), patients who developed a relapse after CR (n = 18), patients who disease progressed after PR (n = 13) and one patient who experienced a relapse during treatment.

The average costs of patients without relapse/progression were € 5,832 (median € 1,516; range € 74 – € 50,690). The mean discounted costs were € 5,686. The main cost drivers were hospitalization (62%), outpatient visits (11%) and diagnostic procedures (9%). Reasons for hospitalization for these patients in disease remission were: cardiac failure after CHOP (n = 4), sepsis/fever immediately after CHOP (n = 2), suspected relapse (n = 1), ileus after CHOP (n = 1), acute secondary leukemia (n = 1) and waiting for a place in a nursing home (n = 1).

The 48 patients in the relapse/progression group together had 52 cases of disease recurrence or progression. Eight patients did not receive any second-line treatment and the other 44 episodes were treated by 26 different treatment options, varying from radiotherapy, chlorambucil, CHOP-like regimens, ifosfamide-based regimens and various other chemotherapy regimens. None of these elderly patients received high-dose chemotherapy followed by stem cell transplant. As a result of the divergent treatments, the costs showed wide variations. The mean follow-up costs of these patients were € 15,224 (median € 14,281; range € 1,115 – € 53,925). The mean discounted costs were € 14,811. The main cost drivers were days of hospitalization (46%), medication (18%) and diagnostic procedures (9%). The most common reasons for hospitalization were administration of second-line chemotherapy and general illness.

Costs outside the hospital were collected until the 18 month of follow-up. For patients in remission, the average costs per month were € 58: € 12 for visits to general practitioner, € 6 for community nurse and € 40 for home assistance. For patients in progression or relapse, the average costs per

month were € 67: € 28 for visits to the general practitioner, € 30 for community nursing and € 9 for home help. Assuming that the average monthly resource use during this period is also valid for the period in which no data were collected, the average costs were € 1,384 (discounted € 1,330) for patients who remained in remission and € 883 (discounted € 849) for patients who experienced relapse or progression. (Patients with progression or relapse on average died earlier, so the total costs were lower).

Cost-effectiveness

A cost-effectiveness ratio was not calculated. The clinical trial showed no benefits in major outcome measures for either of the treatment options. Since the addition of G-CSF to CHOP induced extra costs of € 6,178 (costs in hospital plus medication, 95% CI of the difference = + € 3,050 / + € 9,307)[1] at no extra benefit, the conclusion that this treatment is not cost-effective compared to standard CHOP seems justified.

Discussion

The present study is the first large scale cost analysis performed alongside a randomized clinical trial on first-line standard treatment for aggressive NHL. It was based on a subset of patients from the clinical trial, and this subgroup appeared to be representative of all patients in the clinical trial with respect to relevant patients' characteristics, response to treatment and overall and event-free survival at 1, 2 and 3 years after randomization. The cost calculations provide a good insight into the cost of first-line CHOP treatment in elderly patients with aggressive NHL in the Netherlands. Due to differences in cost per unit, the extrapolation of absolute costs to other countries is difficult. However, the reported volumes of resource utilization are useful in other countries. These data might also be used in economic models. Since CHOP has been the standard treatment for almost three decades, it is unlikely that the treatment of these patients in the setting of a clinical trial exerted a major influence on the medical consumption. At least for the period of first-line treatment, the resource use of the patients reflects the standard clinical practice in the Netherlands. However, a slight increase in costs during CHOP treatment due to trial participation cannot be excluded.(30)

The results of first-line treatment in both arms were identical with respect to CR rate and event-free, disease-free and overall survival. Therefore, a difference in costs during follow-up seems unlikely. We decided not to distinguish follow-up costs according to initial trial arm, but to separate the

[1] When costs outside the hospital are also considered, the total cost difference is € 6,428. A 95 % CI cannot be calculated for this total difference because the costs outside the hospital were collected from another sample of patients.

costs of follow-up in two groups on the basis of response: patients who did not show any relapse or progression and patients who had recurrent or progressive disease. With respect to second-line treatment at the time of disease progression or relapse, a large variation in treatments in these elderly patients was observed. The differences of preferences for second-line treatment among the participating hospitals were reflected in a wide variation of costs during follow-up. From an economic point of view the choice of treatment for elderly relapsing patients might therefore be a very interesting topic for future research.

In this study G-CSF had no important clinical benefits in terms of CR rate and survival, as has also been reported previously.(16, 19, 31) The prophylactic use of G-CSF was beneficial in reducing the infection rate, although no reduction in more severe infections (WHO grade III and IV) was observed. G-CSF prophylaxis resulted in less antibiotic prescriptions, but no decrease in hospital admissions. The additional costs of G-CSF were only in part counterbalanced by fewer antibiotic prescriptions, and the overall costs of CHOP plus G-CSF were significantly higher than those of CHOP alone.

The American Society of Clinical Oncology (ASCO) guidelines on the use of hematopoietic colony-stimulating factors (CSF) do not recommend primary prophylactic CSF. In special circumstances, such as treatment of elderly patients, CSF might be considered, although its benefits have not been determined.(32) The National Comprehensive Cancer Network (NCCN, USA) recommended the prophylactic use of hematopoietic growth factors for patients aged 70 and older.(33) The European Organization for Research and Treatment of Cancer (EORTC) guidelines for the use of CSF in elderly patients with cancer recommend prophylactic G-CSF for all elderly patients receiving curative therapy.(34) These recommendations were largely based on the major reduction in neutropenia observed with G-CSF administration, and the reduced number of neutropenic infections. No randomized study has shown any benefit in survival, or a reduction in toxic deaths. With an expanding older population, and an increasing incidence of NHL, the standard use of prophylactic G-CSF could have major consequences for the health care budget.

The majority of economic studies on the use of prophylactic G-CSF have been performed in the treatment of small cell lung cancer (SCLC). The first clinical placebo-controlled, randomized trial with primary G-CSF prophylaxis showed an impressive reduction in rates of febrile neutropenia (FN), from 77% to 40%. The incidence of hospitalization was reduced by 50%.(35) A cost analysis was performed in a subgroup of patients . Three health care models were used, resulting in different FN risk thresholds for the costs of G-CSF being less than the costs of FN hospitalization: 35% (charge model), 60% (cost model) and 70% (Medicare model).(36) A cost minimization study concluded that with a risk of FN of > 40% the use of G-CSF was cost-effective.(37) Also taking into account indirect costs during FN, a 20-25% risk of FN has been estimated as a threshold in economic models.(38, 39) In another clinical study comparing G-CSF prophylaxis with placebo in patients with SCLC the incidence of FN was slightly lower.(40) However, the incidence of FN in the placebo-treated patients in these two studies was considerably higher than in standard clinical practice, in which an incidence of FN of 18-19% is reported.(41, 42) Several

reviews on the economic impact of prophylactic G-CSF in the treatment of SCLC have been published.(43, 44) It is clear that the cost-effectiveness of primary G-CSF prophylaxis depends on several factors. It is suggested that elderly patients in particular may benefit from the primary G-CSF prophylaxis.(45) In a survey on the use of prophylactic G-CSF in the USA it was reported that the ASCO guidelines on this topic are supported by > 90% of respondents.(46) In practice, the use of colony stimulating factors was found to deviate from the ASCO guidelines, with wide variation between different oncology practices and even at the level of individual oncologists within a practice.(47) A retrospective study on the treatment of aggressive NHL in a large group of patients reported that 17% of all patients experienced FN, 21% of patients aged > 65 year did so. Only 8% received early G-CSF (started at cycle 1 or 2).(48) Three small studies suggested that adding prophylactic G-CSF to standard chemotherapy would lead to a more cost-effective treatment as compared to standard chemotherapy without G-CSF, particularly in elderly patients.(18, 49, 50) A larger French study that randomized younger patients undergoing 4 cycles of ACVBP or NCVBP chemotherapy (doxorubicin or mitoxantrone, cyclophosphamide, vindesine, bleomycin, methylprednisone) to lenograstim or placebo concluded that adding G-CSF resulted in lower costs, given a lower number of infections and fewer days spent in hospital.(51) However, costs of lenograstim itself were left out of consideration. The cost benefit is no longer present if G-CSF costs are added.

On the basis of the randomized clinical trial in aggressive NHL on which this cost analysis was based, we conclude that the prophylactic administration of G-CSF in elderly patients treated with CHOP cannot be advised as routine prescription. A reduction in infection rate has been demonstrated, but remission and survival rates were not improved and there was a large increase in costs.

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ETOPOSIDE, MITOXANTRONE AND PREDNISONE, A SALVAGE REGIMEN WITH LOW TOXICITY FOR REFRACTORY OR RELAPSED NON-HODGKIN'S LYMPHOMA.

Chapter 6

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Abstract

Background and objectives: Relapsed non-Hodgkin's lymphoma (NHL) is preferably treated with high-dose therapy and stem cell support. However, not all patients qualify for intensive chemotherapy. We evaluated the efficacy and toxicity of a new salvage chemotherapy regimen designed for patients with a relapsed or refractory NHL who are not appropriate candidates for high-dose therapy (HDT).

Design and methods: Seventy-nine patients received a regimen consisting of etoposide (350 mg/m^2 i.v. day 1), mitoxantrone (14 mg/m^2 i.v. day 1) and prednisone (80 mg/m^2 p.o. days 1-5) (EMP). The majority had aggressive NHL. Twenty-one patients were elderly, i.e. >60 years of age.

Results: The overall response rate in the 79 patients was 38% as compared to 67% in the elderly. The progression-free survival was 54% and 30% at 12 months and 24 months, respectively. The toxicity of the regimen was relatively low. No toxic deaths have occurred. In 28 of 231 cycles (12%) a CTC-grade 2-4 infection was encountered. Twenty-one hospital admissions were necessary because of infection or fever. Other toxicity was rare. Toxicity was not greater in elderly patients. WHO performance status 2-4 and elevated serum lactate dehydrogenase (LDH) were adverse prognostic factors for response as well as for overall survival. Another adverse prognostic factor for response was age <60 years.

Interpretation and conclusions: EMP is a new salvage regimen with a relatively low toxicity. It should be considered for patients with a relapsed or refractory NHL who are not candidates for standard reinduction therapy and stem cell transplantation.

Introduction

The standard chemotherapy regimen for aggressive non-Hodgkin's lymphoma (NHL) is CHOP, consisting of cyclophosphamide, doxorubicin, vincristine and prednisone.(1-4) The complete response rate achieved with CHOP as initial treatment is 65% in young adults and 45-60% in older patients.(1, 3, 4) Up to 40% of these patients relapse within two years.(5) Young patients with a chemosensitive relapse may be cured by high dose therapy (HDT), followed by stem cell transplantation (SCT).(6, 7) However, for elderly patients with relapsed NHL effective salvage regimens are hampered by their toxicity.

Several salvage regimens including IMVP-16, DHAP, MIME, CAMP, MVLP and VIM, have been published.(5, 8-12) The results of second-line chemotherapy regimens are, however, disappointing. Although responses may be observed in 35% to 55% of the patients, these are usually of short

duration and less than 15% of patients achieve a durable complete response without SCT.
We used a new regimen in relapsed or refractory patients that is not cross resistant with CHOP. It combines etoposide with mitoxantrone and prednisone (EMP). Etoposide is an epipodophyllotoxin derivative functioning as a topoisomerase II and protein synthesis inhibitor. It is an active drug in NHL, especially in a multidrug combination chemotherapy regimen.(13) Mitoxantrone is a synthetic anthracenedione that inhibits the nucleic acid synthesis. It is an active drug in lymphomas and is well tolerated, even by elderly patients.(3, 14, 15)
Here we describe the results of 79 patients with relapsed or refractory NHL who were treated with EMP.

Design and Methods

Patients

From 1994 to 1998, 79 consecutive patients with relapsed or primary refractory stage II, III or IV NHL, who were considered not to be candidates for HDT, were included in a single institution study for the evaluation of safety and efficacy of EMP-treatment. All patients gave informed consent prior to their inclusion in the study.
Before EMP treatment a new biopsy was obtained from each patient and the histologic diagnosis was revised according to the REAL classification.(16)

Treatment

The EMP-regimen consisted of etoposide 350 mg/m^2 combined with mitoxantrone 14 mg/m^2 intravenously (i.v.) on day 1 and prednisone 80 mg/m^2 orally on days 1 to 5. It was administered at 21-day intervals. In case of severe neutropenia or thrombocytopenia (>WHO grade 2) treatment was postponed for 1 week. Patients were scheduled to receive 3 cycles, after which restaging was performed. Responsive patients then received additional cycles of EMP to a maximum of 6 cycles. Responsive patients who achieved a complete response were allowed to be treated with intensive consolidation therapy, followed by autologous stem cell transplantation. In case of either progressive disease, unacceptable toxicity or severe adverse events, treatment was stopped. The Common Toxicity Criteria were used to classify the treatment related toxicity.(17)

Response Evaluation

A complete response (CR) was defined as the disappearance of all symptoms and signs for at least 4 weeks, without the development of new lesions. A partial remission (PR) was defined as a reduction by at least 50% of all measurable lesions. Progressive disease (PD) was defined as an increase of >25% of tumor mass or appearance of a new lesion during treatment or within 4 weeks after treatment.

Statistical Analysis

Overall survival (OS) was measured from the start of EMP treatment until death. Patients still alive at the time of analysis were censored at the last follow-up date. Progression-free survival (PFS) was calculated for all patients who had reached a PR or CR with EMP treatment, from the date of response until relapse, progression or death, whichever came first. The following patient characteristics at the start of EMP were included in the analysis of prognostic factors: age (up to 60 versus over 60 years), gender, best response on previous chemotherapy, histologic diagnosis (Working Formulation low versus intermediate/high grade), WHO performance status (0-1 versus 2-4) and serum LDH level at the start of EMP (normal versus elevated, i.e. larger than the upper limit of the normal value). Pearson's chi-squared test and Fisher's exact test, whichever appropriate, and logistic regression were used to determine an association between clinical features at the start of EMP and the response to EMP. The Kaplan-Meier method was used to estimate the overall survival and the progression-free survival. The logrank test and Cox regression analysis were performed to study differences in survival between subgroups. All reported P-values are two-sided and a significance level ($\alpha = .05$) was used.

Results

The patient characteristics at the start of EMP therapy are summarized in Table 1. The international prognostic index (IPI), as calculated at presentation with NHL, was low-risk in 35 patients, low-intermediate in 22, high-intermediate in 11 and high in 8 patients.(18) In 3 patients the serum LDH level at presentation was not determined. All patients had received one or more chemotherapy regimens before inclusion in the present study (Table 2). In 61 patients CHOP had been the primary treatment. Thirty-five patients had received two ore more chemotherapy regimens before EMP.

Of the 79 patients who started EMP, 38 patients received at least 3 cycles and 9 patients completed 6 cycles of EMP according to the planned schedule. The main reason for stopping EMP treatment prematurely was progressive disease. The overall response rate was 38%, i.e. 9% CR and 29% PR. The median follow-up of the 27 patients still alive is 14 months. The progression-free survival (PFS) of responding patients is 54% at 12 months and 35% at 24 months from the date of response (Fig. 1). The overall survival at 12 and 24 months is 41% and 31% respectively (Fig. 2a). WHO performance status 2-4 ($P < .001$), elevated serum LDH ($P = .001$) and age below 60 years ($P = .002$) were negative prognostic factors for the probability of achieving a response to EMP therapy. Although the performance status and serum LDH were associated with each other ($P < .01$), they retained a statistically significance in multivariate logistic regression, with $P < .01$ and $P = .03$, respectively. Univariate analysis showed that WHO performance status 2-4 and an elevated serum LDH were strong adverse prognostic factors for overall survival with P-values $< .00001$, and they remained statistically significant in the multivariate Cox regression with $P < .00001$ and $P < .0001$, respectively (Fig. 3a and 3b). There was a trend towards a better survival in patients who had achieved a CR on prior treatment (median survival 17 months with CR versus 5 months without prior CR, $P = .07$).

Table 1: **Patient characteristics**

Characteristics		All patients	≤60 years	>60 years
No. of patients		79	58	21
Age:	Median	53	50	69
	Range	24-77	24-60	61-77
WHO-performance status				
	0-1	56 (71%)	40 (69%)	16 (76%)
	2	15 (19%)	13 (22%)	2 (10%)
	3	7 (9%)	4 (7%)	3 (14%)
	4	1 (1%)	1 (2%)	-
Histopathology*				
	CLL/SLL	1	1	-
	LPL	1	-	1
	MCL	6	3	3
	FCCL grade I	5	5	-
	FCCL grade II	2	2	-
	FCCL grade III	5	3	2
	MALT (small cell)	1	1	-
	Plasmacytoma	1	1	-
	DLBCL	45	31	14
	MF	1	1	-
	PTCL	4	3	1
	ATL	1	1	-
	ALCL	5	5	-
	EATC	1	1	-
Transformation from low grade NHL		13	12	1
No. of extranodal sites				
	0-1	65 (82%)	48 (83%)	17 (81%)
	>1	14 (18%)	10 (17%)	4 (19%)
LDH normal		37 (47%)	26 (45%)	11 (52%)
LDH elevated		42 (53%)	32 (55%)	10 (48%)

* according to the REAL classification (16): CLL: chronic lymphocytic leukemia, SLL: small lymphocytic lymphoma, LPL: lymphoplasmacytoid lymphoma, MCL: mantle cell lymphoma, FCCL: follicular center cell lymphoma, MALT: extranodal marginal zone B-cell lymphoma, DLBCL: diffuse large B-cell lymphoma, MF: mycosis fungoides, PTCL: peripheral T-cell lymphoma, ATL: adult T-cell lymphoma, ALCL: anaplastic large cell lymphoma, EATC: enteropathy associated T cell lymphoma

Table 2: **Treatment before EMP**

	No. of patients								
Therapy	**First line**			**Second line**			**Third line**		
	All	≤60	>60	All	≤60	>60	All	≤60	>60
CHOP	61	43	18	6	4	2	5	5	-
CVP	10	9	1	2	2	-	-	-	-
DHAP	-	-	-	14	13	1	3	3	-
PSCT	-	-	-	1	1	-	1	1	-
Other	8	6	2	12	11	1	2	2	-

CHOP, Cyclophosphamide, doxorubicin, vincristine and prednisone; CVP, Cyclophosphamide, vincristine and prednisone; DHAP, Dexamethasone, high-dose Ara-C, cisplatin; PSCT, high-dose therapy plus peripheral blood stem cell transplantation; Other: fludarabine; pentostatine; chlorambucil; chorambucil plus prednisone; CEMP (cyclophophamide, etoposide, mitoxantrone, prednisone); total body irradiation. Localized radiotherapy as a prior treatment is not included.

Elderly patients usually have a lower response rate and suffer more toxicity on chemotherapy regimens than younger patients. Therefore we analyzed the results in the patients >60 years as a separate group. In the 21 elderly patients the CR and PR rates were 19% and 48% (response rate = 67%) respectively. The overall survival at 24 months was 49% (Fig 2b).

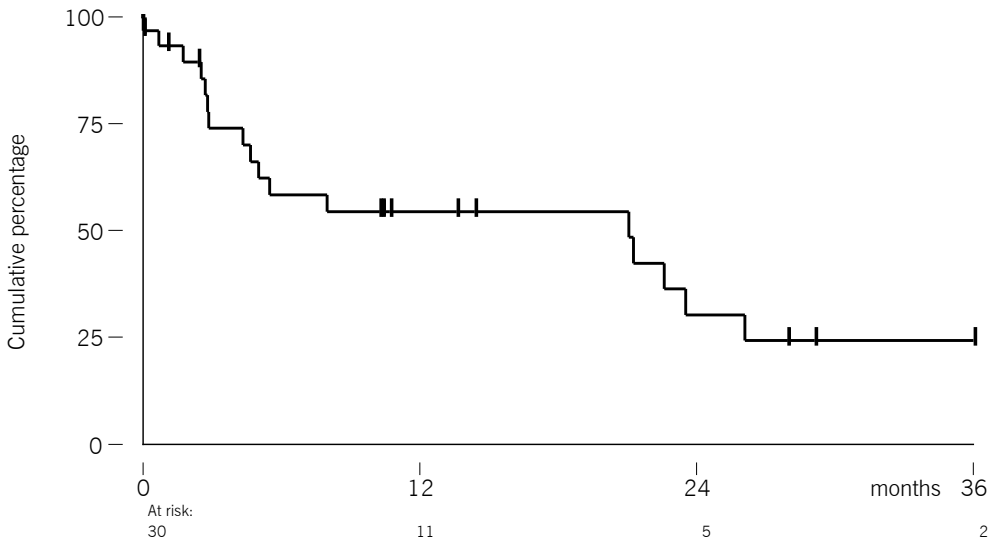

Fig 1. **Kaplan-Meier curve of progression-free survival for patients who achieved a PR or CR on EMP.**

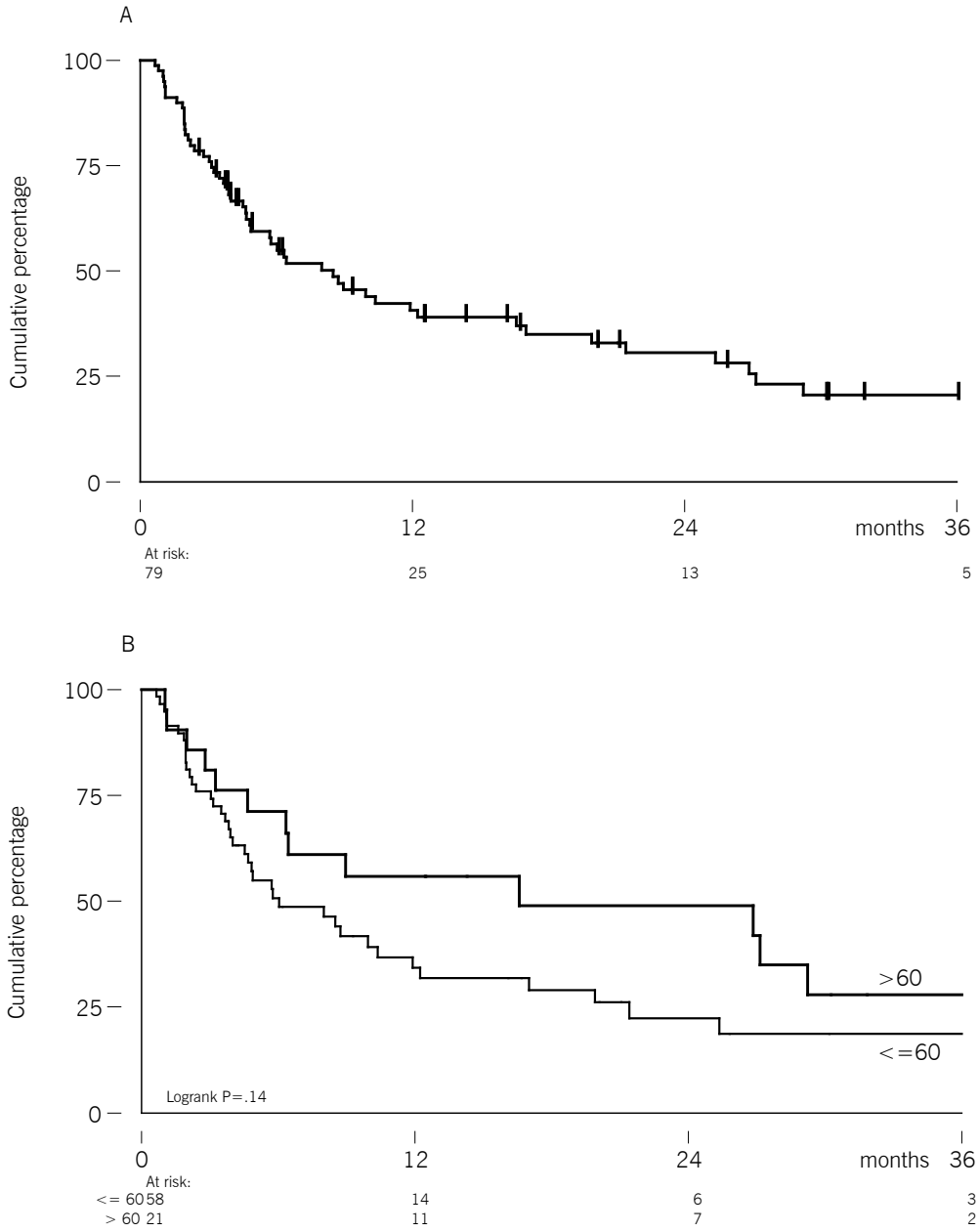

Fig 2. **Kaplan-Meier curve of overall survival.**
A: all patients. B: by age group: ≤ 60 years and > 60 years.

The hematologic toxicity was low, as shown in Table 3. There have been 28 documented infections (Table 4). Thirty patients have been admitted to hospital, 13 because of a documented infection, 8 because of fever of unknown origin, and most others because of progressive disease.

Table 3. **White blood cell and platelet nadirs per EMP cycle**

Cycle	**I**	**II**	**III**	**IV**	**V**	**VI**
Number*	**79 (5)**	**63 (6)**	**38 (6)**	**27 (8)**	**15 (6)**	**9 (4)**
Leukocyte nadir x109/l						
Median	1.2	1.5	1.7	1.5	1.4	1.6
Range	0.1-145	0.1-395	0.2-14.5	0.3-6.0	0.4-16.0	0.8-4.8
Platelet nadir x109/l						
Median	92	108	86	111	83	128
Range	3-691	7-900	8-364	22-326	39-285	75-151

* The number of cycles administered, in brackets the number of cycles of which the nadir is unknown

The patterns of toxicity in the elderly were not different from those in the younger patients. In 11 of the 77 cycles given to elderly patients infections of CTC grade ≥ 2 occurred. Other toxicity exceeding CTC-grade 1 was rarely observed. Gastro-intestinal toxicity was encountered after 3 cycles. One elderly patient presented with cardiac toxicity grade 3 due to heart failure in a period of fever. No neurologic or pulmonary toxicity has occurred. No toxic deaths were observed.

Table 4. **Infections**

	No. of cycles (%)		
Infections*	**All patients**	**≤60 years**	**>60 years**
grade 2	17/231 (7)	12/154 (8)	5/77 (7)
grade 3	9/231 (4)	5/154 (3)	4/77 (5)
grade 4	2/231 (1)	-	2/77 (3)

* according to the Common Toxicity Criteria.(17)

Thirty-five patients received further treatment after EMP. Sixteen patients received radiotherapy, 8 patients received another chemotherapy regimen, 3 received both of these treatments. The clinical condition of 8 responsive patients improved in such a way that it was decided to treat these individuals with HDT followed by autologous blood stem cell transplantation after 3 cycles of EMP.

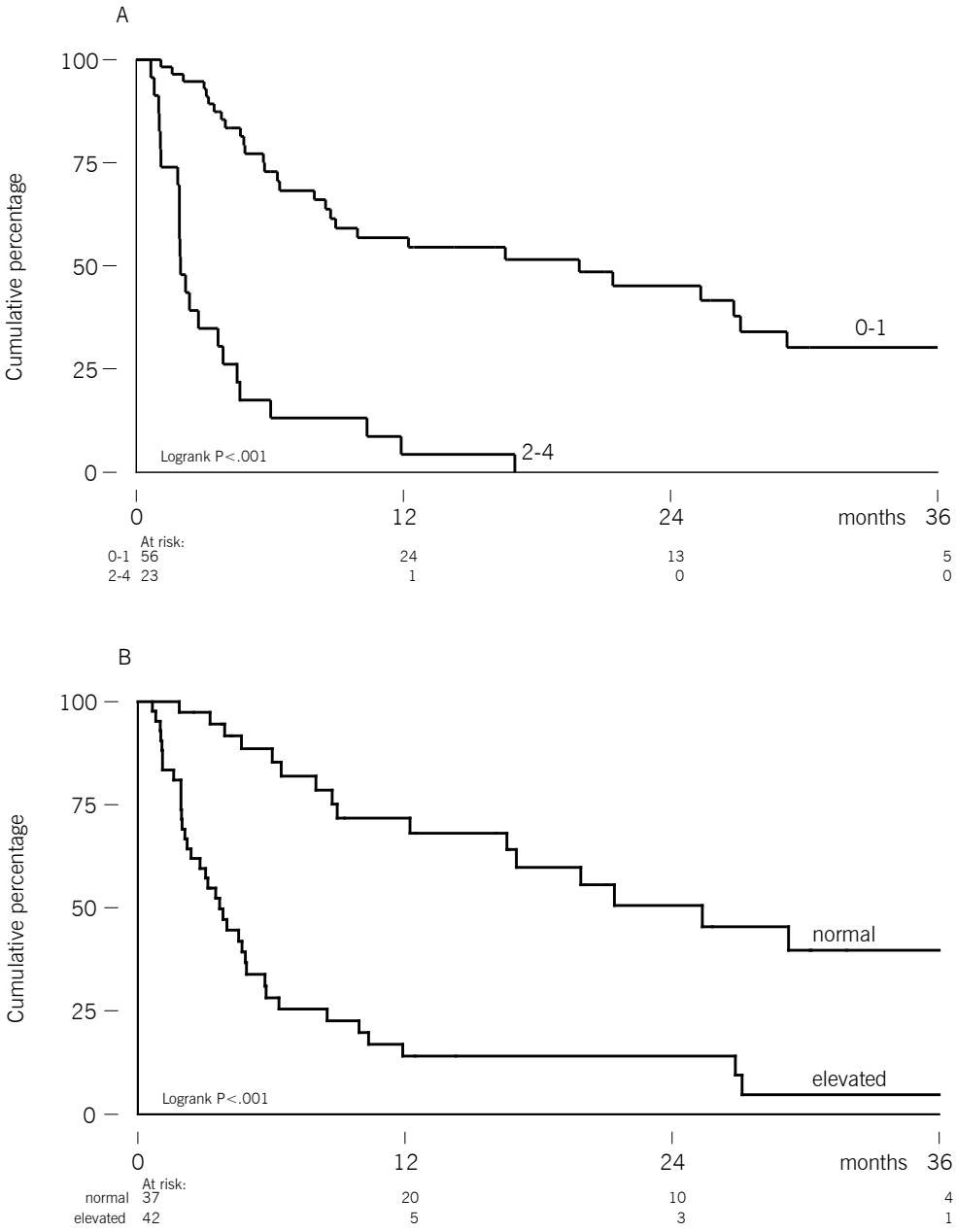

Fig 3. **Kaplan-Meier curve of overall survival by prognostic features. A. WHO performance status 0-1 versus 2-4. B. LDH at start of EMP, normal versus elevated**

Discussion

The EMP regimen consisting of etoposide, mitoxantrone and prednisone proved to be an effective schedule for refractory or relapsed non-Hodgkin's lymphoma, considering these patients did not qualify for HDT and stem cell transplantation. The overall response rate of 38% is comparable to that achieved by other salvage therapies, which have shown response rates of 40 to 60% in pretreated patients.(5, 8-10, 12) In general, regimens that result in a better response rate also have more extensive toxicity, a significant number of toxic deaths and more hospital admissions. In the present study no toxic deaths were observed. Hematologic toxicity was moderate, while no other significant toxicity was observed, even in heavily pretreated patients.

In Table 5 we compare the results of the published trials with etoposide and mitoxantrone. The response rates are comparable between these studies. However, the overall survival of patients in the present study was longer than in the subcategory of pretreated patients in other studies.

Table 5. **Treatment results with etoposide/mitoxantrone chemotherapy regimens**

	Schedule	No. of patients median age (range)	Response rate	Median OS (months)	Remarks
EMP	E: 350 mg/m2 i.v. day 1 M: 14 mg/m2 i.v. day 1 P: 80 mg/m2 p.o. day 1-5	79 53 (24-77)	38%	9	6 cycles q 3 wk, on outpatient basis, 79 pretreated patients, 71 aggressive NHL
MVP (19)	E: 150 mg/m2 i.v. day 1 200 mg/m2 p.o. day 3 + 5 M: 7-9 mg/m2 i.v. day 1 P: 25 mg p.o. day 1-5	54 75 (64-93)	50%	9	6 cycles q 3-4 wk, on outpatient basis, 14 pretreated, patients, 9 aggressive NHL
PEN (20)	E: 50 mg p.o. day 1-4 M: 8 mg/m2 i.v. day 1 P: 50 mg/m2 p.o. day 1-14	35 75 (67-92)	37%	4+	6 cycles q 4 wk, on outpatient basis, 8 pretreated, patients 8 aggressive NHL
VMP (21)	E: 80 mg/m2 p.o. day 1-5 M: 8-10 mg/m2 i.v. day 1 Pm:80 mg/m2 p.o. day 1-5	48 76 (71-92)	58%	17	3-9 cycles q 3 wk, on outpatient basis, 12 pretreated patients, 12 aggressive NHL
VIM (12)	E: 65 mg/m2 i.v. day 1-3 M: 3 mg/m2 i.v. day 1-3 I: 650 mg/m2 i.v. day 1-3 (+ Me: 300 mg 3x/day)	55 66 (18-89)	41%	14	as much cycles as needed q 3 wk, 3 days in hospital, 55 pretreated, patients 33 aggressive NHL

E: etoposide, M: mitoxantrone, P: prednisone, Pm: prednimustine, I: ifosfamide, Me: mesna

In patients aged 50-65 years treatment-related mortality (TRM) of HDT and autologous transplantation is double that in patients <50 years.(22) Many institutions do not include patients > 60 years of age in a transplant program. Therefore, we analyzed response and toxicity in the small subgroup of patients over 60 years old separately. These elderly patients responded well to EMP and no differences from younger patients were observed. It should be emphasized that the younger patients generally had received more extensive pretreatment. Indeed, 34% of the younger patients had received 2 and 19% had received 3 prior regimens. Only 19% of the elderly patients had received 2 prior regimens (Table 2).

The main reason for stopping EMP-treatment prematurely was progressive disease. Within these limits, 29% of the elderly, as opposed to 5% of the younger patients, could complete all 6 cycles of EMP. The majority of these patients completed the treatment at the cost of only minor toxicity, which did not increase with age. .

WHO performance status 2-4 and elevated serum LDH before the first EMP cycle were significant adverse prognostic factors for survival and response. It is well known that the LDH level is an important indication of tumor mass and turnover. Poor performance status and elevated LDH are adverse prognostic factors in the IPI(18). In this study none of the patients with both performance status >1 and elevated LDH responded to the treatment (14 patients ≤60 years, 4 patients >60 years).

In conclusion, the EMP regimen is well tolerated and can easily be administered on an outpatient basis. It seems especially adequate as a salvage regimen for patients who do not qualify for HDT, because of the acceptable toxicity and relatively long median survival it produces in these patients. WHO performance status and serum LDH are valuable predictors of response and survival in order to select those patients most likely to benefit from EMP salvage therapy.

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SUMMARY AND CONCLUDING REMARKS

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SAMENVATTING

Chapter 7

Summary and concluding remarks

The treatment of elderly patients with an aggressive non-Hodgkin's lymphoma has gradually changed over the last decades. The first publications concerning elderly patients with lymphoma emphasized the increased toxicity and poor outcome of this patient group.(1-3) The aim of many subsequent studies has been to decrease toxicity.(4-6) Most of these studies however reported decreased response rates and deterioration of survival if age adapted therapy was used. It also became evident that doxorubicin proved to be a toxic, but essential drug in any regimen prescribed with a curative intention.(7-9)

The development of recombinant granulocyte colony-stimulating factor (G-CSF) raised expectations that this growth factor could improve the results of therapy because it would become possible to maintain the dose-intensity of the chemotherapy regimen by inducing rapid hematopoietic recovery.(10) Moreover, a shorter duration of the neutropenic phase could probably reduce the incidence of neutropenic fever, bacterial infections and the number of hospital admissions.(11, 12)

In the current thesis the results of a large prospective multicenter clinical trial are reported. This trial was designed to investigate if prophylactic G-CSF administration could improve the poor results of treatment in elderly patients with an aggressive non-Hodgkin's lymphoma. The primary question was whether a higher relative dose-intensity would lead to improved treatment outcome. Secondary endpoints were the quality of life and the cost-effectiveness associated with such treatment. This trial was supported by the Dutch government (Ontwikke lingsgeneeskunde 95-004)

In chapter 2 the clinical results of this multicenter phase III study are reported. The patients received standard CHOP every 3 weeks or the same regimen with prophylactic administration of G-CSF during 10 days following CHOP. With strict adherence to the protocol guidelines for dose delay and dose reductions, it became evident that most patients could tolerate standard 3-weekly CHOP. A small but significant improvement of dose-intensity with G-CSF is obtained, but this has no effect on the outcome of treatment. The number of infections is reduced as a result of prophylactic G-CSF, but the most severe infections occur at the same rate in both treatment arms. The quality of life did not change with G-CSF compared to standard CHOP. These data illustrate that standard prophylactic use of G-CSF is not warranted in this age group.

The publication of this study has resulted in discussions about the reasons of the poor prognosis of elderly patients, and proposals of other measurements that could be used to improve the outcome. Chapter 3 contains in brief some aspects of such a discussion.

Chapter 4 focuses on the question whether and to what extent the quality of life is affected over time by this treatment with strict protocol guidelines. The prophylactic G-CSF administration has no effect on the quality of life. The changes of quality of life parameters over time show some

remarkable patterns. Global quality of life before the start of treatment is more impaired in patients with a higher age-adjusted prognostic index score. After the start of treatment patients with a lower prognostic index and a better quality of life report a decrease in functioning. The patients with a higher prognostic index and a quality of life that already was lower before treatment do not report a further decrease in functioning. After finishing treatment the quality of life of those patients that obtain a partial response or complete remission returns to pretreatment levels or higher. The most important long term side-effect was peripheral neuropathy.
The costs of treatment of elderly patients treated with CHOP have been analyzed and they are described in chapter 5. The addition of G-CSF increases the cost of treatment with 50%, from €12,000 to €18,000. No major change in outcome is observed, so a cost-effectiveness ratio is not calculated. Since the addition of G-CSF to CHOP induced extra costs at no benefit, the conclusion that this treatment is not cost-effective compared to standard CHOP seems justified.
While the complete remission rate after CHOP is still only 50%, and relapses are frequent, the need for an effective but non-toxic second-line regimen for patients not eligible for intensive therapy and stem cell transplantation is urgent. The results of a regimen consisting of etoposide, mitoxantrone and prednisone (EMP) are presented in chapter 6. The toxicity of this regimen is low, especially when the age and/or the extensive prior treatment of the patients is taken into account. 10% of the cycles were complicated by an infection. No toxic deaths occurred. In the subgroup of elderly patients toxicity was not higher than in the younger patients. The 2-year survival in these patients was 45%.

The results of the studies in this thesis prompt the question of the role of G-CSF in the treatment of elderly patients. Routine prophylactic administration of G-CSF with standard 3-weekly CHOP can not be advised. However, G-CSF can play an essential role if the aim is to increase the dose-intensity of CHOP much more. Recently an improved response and survival has been reported in elderly patients with the administration of CHOP every 2 weeks (CHOP-14).(13) This dose-intensity is impossible without administration of G-CSF. The improvement of the outcome with CHOP-14 compared to CHOP-21 confirms that a major increase in dose intensity (a 50% increase) indeed is important and has a beneficial effect on survival.

In the past few years the developments in diagnosis and treatment of diffuse large B-cell lymphoma (DLBCL) have been enormous. Gene-expression profiling of DLBCL has identified clusters with a different response to standard treatment.(14-17) Routine application of this technique is very expensive. One of the alternatives for the analysis of a large amount of samples is the use of tissue micro-array with immunohistochemical staining of protein expression.(18-20) If the results of these studies prove to be consistent in determining the subgroup of DLBCL, the next step will be to investigate the optimal therapy for each subgroup. A better understanding of the specific changes on the molecular level of the malignant lymphoma cell may ultimately result in the development of targeted therapy.

The clinical use of monoclonal antibodies has been considered very promising. These great expectations have come true with the chimeric anti-CD20 monoclonal antibody rituximab. At the moment rituximab is a part of the treatment of many CD20-positive lymphomas. Two large prospective studies with rituximab-CHOP (R-CHOP) in diffuse large B-cell lymphoma observed major improvements in response rate and survival.(21, 22) It should be mentioned that this improvement of outcome for the first time was reported in elderly patients. However, the costs of treatment of diffuse large cell lymphoma have increased significantly with the introduction of rituximab. A cost-effectiveness study has calculated that the addition of rituximab resulted in a discounted cost increase of € 15,350 to the costs of CHOP, and the costs per discounted QALY gained in elderly patients (> 60) € 17,933, and in younger patients € 13,983.(23) It is suggested that this cost-effectiveness ratio is acceptable, given the severity of the disease.

Other monoclonal antibodies, i.e. alemtuzumab (anti-CD52) will be studied in combination therapy of T-cell lymphomas. Many questions however are still unanswered. The role of maintenance therapy with monoclonal antibodies needs to be addressed in further studies. The radiolabeled monoclonal anti-CD20s (Yttrium-90 ibritumomab, or Iodine-131 tositumomab) have shown to be effective in the treatment of relapsed follicular and transformed lymphomas.(24-28) Moreover, ibritumomab was superior to rituximab in the treatment of relapsed follicular lymphoma.(29) Its role in the treatment of DLBCL is under study now.

When the early results of the CHOP-14 and R-CHOP regimens in elderly patients became known the HOVON has embarked on a prospective cooperative phase III trial in elderly patients with DLBCL. All patients will receive CHOP chemotherapy at brief intervals of 2 weeks (CHOP-14), which is supported by G-CSF. The patients are randomly assigned to rituximab as an additional treatment modality. This study will reveal whether the combination of the two strategies, i.e. dose-intensification and immunotherapy can improve the outcome of treatment in elderly patients.

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Samenvatting

De behandeling van oudere patiënten met een agressief non-Hodgkin lymfoom is de laatste decennia geleidelijk veranderd. De eerste publicaties over oudere patiënten met een maligne lymfoom benadrukten de toegenomen toxiciteit en slechte uitkomst van deze patientengroep.(1-3) Hierna hebben veel studies zich gericht op het verminderen van de toxiciteit.(4-6) De meeste van deze studies beschreven vervolgens verminderde response rates en slechtere overleving bij voor de leeftijd aangepaste therapie. Het werd ook duidelijk dat doxorubicine een toxisch, maar essentieel middel was in elk regime met een curatieve intentie.(7-9)

De ontwikkeling van recombinant granulocyt kolonie-stimulerende factor (G-CSF) deed de hoop rijzen dat deze groeifactor de resultaten van de therapie zou kunnen verbeteren, omdat het mogelijk zou worden de dosisintensiteit van het chemotherapie schema te handhaven door snel hematopoietisch herstel.(10) Verder zou een kortere neutropene fase de incidentie van neutropene koorts, bacteriële infecties en het aantal ziekenhuis opnames mogelijk kunnen reduceren.(11, 12)

In dit proefschrift zijn de resultaten van een grote prospectieve multicenter klinische studie beschreven. Deze studie was ontwikkeld om te onderzoeken of profylactische toediening van G-CSF de slechte resultaten van de behandeling van oudere patiënten zou kunnen verbeteren. De belangrijkste vraag was of dankzij toediening van G-CSF een hogere dosisintensiteit zou worden bereikt en daarmee een beter behandelingsresultaat. Ook werd de kwaliteit van leven en de kosteneffectiviteit van de behandeling onderzocht. De studie werd financieel ondersteund als Ontwikkelingsgeneeskunde studie (OG 95-004).

In hoofdstuk 2 zijn de klinische resultaten van deze multicenter fase III studie beschreven. De patiënten werden behandeld met standaard CHOP elke 3 weken, of hetzelfde regime met profylactische toediening van G-CSF gedurende 10 dagen na de CHOP. Bij een strikt volgen van de protocol richtlijnen betreffende dosis uitstel en dosis aanpassing werd duidelijk dat de meeste patiënten 3-wekelijkse standaard CHOP konden verdragen. Een kleine maar significante verbetering van de dosisintensiteit bij gebruik van G-CSF werd wel bereikt, maar dit had geen effect op de uitkomst van de behandeling. De patientengroep die profylactisch G-CSF kreeg ontwikkelde minder infecties, maar de meest ernstige infecties kwamen in beide patientengroepen even vaak voor. De kwaliteit van leven veranderde niet bij de patiënten met G-CSF, in vergelijking met de patiënten die alleen standaard CHOP ontvingen. Uit deze gegevens kan geconcludeerd worden dat het profylactische gebruik van G-CSF in deze patientengroep niet geïndiceerd is.

De publicatie van deze studie heeft geleid tot discussies over de oorzaken van de slechte prognose van oudere patiënten, en voorstellen tot andere maatregelen die de uitkomst zouden kunnen verbeteren. Hoofdstuk 3 bevat in het kort enkele aspecten van een dergelijke discussie.

In het onderzoek beschreven in hoofdstuk 4 wordt onderzocht of en in welke mate de kwaliteit van leven beïnvloed wordt door de behandeling met CHOP op geleide van strikte protocollaire richtlijnen. De profylactische G-CSF toediening had geen effect op de kwaliteit van leven. In de loop der tijd vertoonden de kwaliteit van leven parameters enkele opmerkelijke patronen. De algemene kwaliteit van leven voor start van de behandeling was meer verlaagd bij patiënten met een hogere age-adjusted prognostische index. Na start van de behandeling vermeldden de patiënten met een lagere prognostische index en een betere kwaliteit van leven een afname in functioneren. De patiënten met een hogere prognostische index en een kwaliteit van leven die al lager was voor start van de behandeling rapporteerden geen verder afname in functioneren. Na afronding van de behandeling keerde de kwaliteit van leven terug naar het niveau van voor de behandeling of hoger, bij die patiënten die een partiele respons of complete remissie bereikten. De meest belangrijke bijwerking op langere termijn was perifere neuropathie.
De kosten van de behandeling van oudere patiënten die met CHOP worden behandeld zijn beschreven in hoofdstuk 5. De toevoeging van G-CSF verhoogde de kosten van de behandeling met 50%, van € 12,000 tot €18,000. Er was geen belangrijke verandering in uitkomst, dus er is geen kosteneffectiviteit ratio berekend. Omdat de toevoeging van G-CSF aan CHOP extra kosten genereerde, zonder dat daar winst tegenover stond, is de conclusie gerechtvaardigd dat deze behandeling in vergelijking met standaard CHOP niet kosteneffectief is.
Intussen is het complete remissie percentage na CHOP nog steeds slechts 50%, en treedt frequent een recidief op. Er is dus dringend een effectief maar niet-toxisch tweedelijns schema nodig voor patiënten die niet in aanmerking komen voor intensieve therapie en stamcel transplantatie. De resultaten van een regime dat bestaat uit etoposide, mitoxantrone en prednison (EMP) zijn beschreven in hoofdstuk 6. De toxiciteit van dit regime was laag, vooral wanneer de leeftijd en/of de uitgebreide voorbehandeling van de patiënten in aanmerking werd genomen. 10% van de cycli werd gecompliceerd door een infectie. Er overleden geen patiënten ten gevolge van toxiciteit. In de subgroep van oudere patiënten was de toxiciteit niet hoger dan bij de jongere patiënten. De 2-jaars overleving bij deze patiënten bedroeg 45%.

De resultaten van de studies in dit proefschrift doen de vraag rijzen naar de waarde van G-CSF bij de behandeling van oudere patiënten. Routinematig toedienen van G-CSF bij 3-wekelijks standaard CHOP kan niet worden geadviseerd. Maar G-CSF is essentieel als het doel is om de dosisintensiteit van CHOP veel meer te verhogen. Recent zijn een verbeterde respons en overleving gerapporteerd bij oudere patiënten waarbij CHOP a 2 weken werd toegediend (CHOP-14).(13) Deze dosisintensiteit is onmogelijk zonder ondersteuning met G-CSF. De verbetering in uitkomst met CHOP-14 in vergelijking met CHOP-21 bevestigt dat een belangrijke verhoging van de dosisintensiteit (een toename van 50%) belangrijk is en daadwerkelijk een gunstig effect heeft op de overleving.

In de laatste jaren zijn de ontwikkelingen rondom diagnose en behandeling van diffuus grootcellig B-cel lymfoom (DLBCL) enorm geweest. Genexpressie profielen van DLBCL hebben clusters met een verschillende respons op standaard behandeling geïdentificeerd.(14-17) Routinematige toepassing van deze techniek is erg duur. Een van de alternatieven voor de analyse van grote hoeveelheden monsters is het gebruik van “tissue micro-array” met immuunhistochemische kleuringen van eiwitexpressie.(18-20) Wanneer de resultaten van deze studies consistent blijken te zijn in het bepalen van de subgroep DLBCL, dan kan de volgende stap zijn de optimale therapie voor elke subgroep te bepalen. Een beter begrip van de specifieke veranderingen van de maligne lymfoom cel op moleculair niveau kan uiteindelijk leiden tot de ontwikkeling van specifieke (“targeted”) therapie.

Een veelbelovende modaliteit in de kliniek is het gebruik van monoklonale antistoffen geweest. Deze hoge verwachtingen zijn bewaarheid geworden met de chimere anti-CD20 monoklonale antistof rituximab. Momenteel is rituximab onderdeel van de behandeling van de meeste CD20-positieve lymfomen. Twee grote prospectieve studies met rituximab-CHOP (R-CHOP) in DLBCL toonden grote verbeteringen van response percentage en overleving aan.(21, 22) Opgemerkt moet worden dat deze verbetering in uitkomst voor het eerst bij oudere patiënten is gerapporteerd. De kosten van de behandeling van DLBCL zijn wel significant toegenomen met de introductie van rituximab. Een kosteneffectiviteit studie heeft berekend dat de toevoeging van rituximab leidt tot een toename van verdisconteerde kosten van € 15,350 aan de kosten van CHOP, en de kosten per verdisconteerde QALY (quality adjusted life year) winst bij oudere patiënten (> 60) € 17,933, en bij jongere patiënten € 13,983.(23) Men oordeelt dat deze kosteneffectiviteitsratio acceptabel is, mede gezien de ernst van de ziekte.

Andere monoklonale antistoffen, b.v. alemtuzumab (anti-CD52), zullen onderzocht worden in combinatie-therapie bij T-cel lymfomen. Veel vragen zijn vooralsnog onbeantwoord. De rol van onderhoudstherapie met monoklonale antistoffen dient in studies onderzocht te worden. De radioactief gelabelde monoklonale anti-CD20s (Yttrium-90 ibritumomab, of Jodium-131 tositumomab) zijn effectief bij de behandeling van recidief folliculaire en getransformeerde lymfomen.(24-28) Ook is ibritumomab effectiever dan rituximab bij de behandeling van recidief folliculair lymfoom.(29) De rol van ibritumomab bij de behandeling van DLBCL is momenteel onderwerp van een klinische studie.

Toen de eerste resultaten van het CHOP-14 en het R-CHOP schema bij oudere patiënten bekend werden is de HOVON gestart met een prospectieve fase III studie bij oudere patiënten met een DLBCL. Alle patiënten krijgen CHOP chemotherapie met een kort interval van 2 weken (CHOP-14), met G-CSF support. De patiënten worden gerandomiseerd voor al of niet rituximab als aanvullende behandelingsmodaliteit. Deze studie zal duidelijk maken of combinatie van de twee strategieën, nl. dosis-intensificatie en immunotherapie de uitkomst van behandeling in oudere patiënten kan verbeteren.

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Abbreviations

AAPI	age-adjusted Prognostic Index
ABC	activated B-cell type
AIDS	acquired immunodeficiency syndrome
ASCO	American Society of Clinical Oncology
BNLI	British National Lymphoma Investigation
CNS	central nervous system
CR	complete remission
CT	computed tomography
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
18FDG-PET	18-fluoro-2-deoxyglucose positron emission tomography
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLIPI	Follicular Lymphoma International Prognostic Index
GCB	germinal center B-cell
G-CSF	granulocyte colony-stimulating factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GM-CSF	granulocyte macrophage colony-stimulating factor
HAART	highly active anti-retroviral therapy
HIV	human immunodeficiency virus
HOVON	Dutch-Belgian Hemato-Oncology Cooperative Group
Hp	helicobacter pylori
HTLV-1	human T-cell leukemia virus-1
IMTA	institute of Medical Technology Assessment
IPI	International Prognostic Index
LDH	lactate dehydogenase
MALT	mucosa- associated lymphoid tissue
MBR	major breakpoint region
MRI	magnetic resonance imaging
NHL	non-Hodgkin's lymphoma
NR	no response
PCR	polymerase chain reaction
PD	progressive disease
PR	partial response
QoL	quality of life
QALY	quality adjusted life year
RDI	relative dose intensity
REAL	Revised European-American Classification of Lymphoid neoplasms
SCLC	small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results
SWOG	Southwest Oncology group
WF	Working Formulation
WHO	world health organization

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Curriculum vitae

De auteur van dit proefschrift werd op 14 december 1961 in Delft geboren. Na het behalen van het gymnasium β diploma aan de Rijksscholengemeenschap Koning Willem II te Tilburg werd in 1980 gestart met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. In februari 1987, na het artsexamen (cum laude), kwam zij in dienst van het Havenziekenhuis te Rotterdam, als arts-assistent op de afdeling interne geneeskunde. In juli 1988 kon zij starten met de opleiding interne geneeskunde (opleider: prof.dr. P.C. Stuiver). Vanaf juli 1990 werd de opleiding tot internist vervolgd in het Academisch Ziekenhuis Rotterdam-Dijkzigt (opleider: prof.dr. M.A.D.H. Schalekamp), leidend tot de registratie als internist op 1 juli 1993. Hierna kon zij de opleiding in het aandachtsgebied hematologie starten op de afdeling hematologie, Academisch Ziekenhuis Rotterdam-Dijkzigt (opleider: prof.dr. B. Löwenberg). Aansluitend bleef zij werkzaam op deze afdeling. In januari 1997 werd zij coördinator van het Ontwikkelingsgeneeskunde project "Effect of recombinant G-CSF on the result of chemotherapy (CHOP) in elderly patients with intermediate/high-grade non-Hodgkin's lymphoma". De resultaten van dit project zijn de basis voor dit proefschrift. Van oktober 1998 tot oktober 1999 werkte zij in het hematology researchlab van Dr. P. Greenberg, Stanford University, Palo Alto, USA. Na terugkomst in Rotterdam werd zij staflid op de afdeling hematologie van het Academisch Ziekenhuis Rotterdam-Dijkzigt, later Erasmus MC Rotterdam. Sinds 2001 is zij werkzaam op de lokatie Daniel den Hoed, waar zij o.a. medisch coördinator van de kliniek is. Zij is gehuwd met Teun van Gelder en zij hebben twee zonen, Paul en Mark.

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