Colophon

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Economic Evaluations in Aggressive Non-Hodgkin's Lymphoma

Economische evaluaties bij het agressief non-Hodgkin lymfoom

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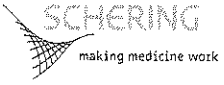

Contents

Preface

Non-Hodgkin's lymphoma (NHL) has the highest incidence rate of all haematological malignancies in the Western world[1]. In the USA, the number of deaths attributable to NHL currently ranks in the top five of cancer related deaths[2]. In the Netherlands, haematological malignancies rank 8 in the cancer incidence list, and about 2100 inhabitants per year are newly diagnosed with NHL[1]. Between 1973 and 1989, the incidence of NHL increased by nearly 60% in the United States, which is one of the largest increases observed in any cancer[3]. This rise has not stopped yet: NHL is amongst the small number of malignancies that also have shown markedly increased incidence and mortality rates during the recent past[2, 4]. During the same years, health care costs in developed countries have risen faster than the general inflation rate, making economic evaluations an integral part of health care decision making[5]. These developments underline the need for economic evaluations of NHL, and this thesis will therefore focus on this kind of evaluations in the most prevalent subtype of NHL.

Some basics about (aggressive) non-Hodgkin's lymphoma

NHL is a lymphoid malignancy, which may manifest itself both within and outside the lymphatic system. The group of NHL consists of a variety of different subtypes, of which the so called 'aggressive NHL' is the most prevalent, which is actually also a generic term for a category of lymphoid malignancies primarily consisting of diffuse large B-cell lymphomas. The diagnosis NHL can only be made on the basis of a histological biopsy sample of an enlarged lymph node, an infiltrated organ, or bone marrow. For the histologic classification, several systems have been used during the past decades. Advanced technological possibilities and improved histologic and molecular-biologic insights have now and again led to the introduction of more sophisticated histology classification systems, as these developments showed heterogeneity within classes of former systems. Issued in 1982, the so-called 'Working Formulation' was one of the most important systems, as it has been the leading histology classification system for many years[6]. In 1994, a new system was proposed: the 'Revised European-American classification of lymphoid neoplasms' (REAL), which distinguished lymphomas on the basis of morphologic, immunologic, cytogenetic and molecular-biologic characteristics[7]. In 1999, a proposal for a World Health Organization (WHO) classification was issued, which is actually a refined version of the REAL classfication[8]. Its definitive version was published by the WHO and the International Agency for Research on Cancer (IARC) in 2001[9].

The extent to which NHL has spread throughout the body is indicated by the Ann-Arbor classification, a staging system that was originally developed in 1971 for Hodgkin's lymphoma[10]. In short, the system distinguishes the following tumour stages: stage I, involvement of 1 lymph node or 1 extranodal organ or site; stage II, $\geq$2 lymph nodes on one side of the diaphragm or 1 extranodal organ or site plus $\geq$1 involved lymph node on one side of the diaphragm; stage III, lymph nodes involved on both sides of

the diaphragm; stage IV, diffuse or disseminated infiltration of ≥1 extranodal organs or sites. The lymphatic system consists of all lymph nodes, the spleen, the thymus, Waldeyer's ring, Peyer's patches, and the appendix.

Combination chemotherapy has transformed aggressive NHL from a fatal disease into one that is often curable[11]. The survival of patients with stage I aggressive NHL (localised disease) is however very different from the survival of patients with stage II-IV NHL (disseminated disease). Five-year overall survival of patients with stage I aggressive NHL is 80-90% after optimal therapy[12, 13]. The approximate 5-year survival rate in patients with stage II-IV aggressive NHL is 50%, varying from 25% to 75%, depending on the risk factors at diagnosis[11]. This thesis will focus on patients with stage II-IV aggressive NHL.

The prognostic significance of a number of risk factors at initial diagnosis was demonstrated in 1993[11]. Since then, this 'International Prognostic Index for Aggressive NHL' (IPI) has been used worldwide in almost all studies on aggressive NHL. The IPI distinguishes 5 factors, which have been shown to be associated with favourable vs. unfavourable effects on survival: age ≤60 years vs. >60 years, Ann-Arbor stage I/II vs. III/IV, serum lactate dehydrogenase (LDH) concentration ≤1x normal vs. >1x normal, performance status 0/1 (ambulatory) vs. 2-4 (not ambulatory), and the number of extranodal sites involved by NHL ≤1 site vs. >1 site. The IPI system also comprises two sum scores (the standard index and the age-adjusted index), resulting from these 5 factors and distinguishing 4 risk profiles according to survival.

When a patient is diagnosed with stage II-IV aggressive NHL, treatment will be initiated immediately. Standard first-line therapy has been CHOP (an acronym for a chemotherapy regimen consisting of cyclophosphamide, hydroxyldaunomycin, oncovin, and prednisone) ever since 1976[14]. Patients will receive 6 to 8 cycles, usually every 21 days, depending on their response. Radiotherapy can consequently be applied on NHL localisations that were initially 'bulky' (>10 cm in diameter). In case of relapse or resistance of the NHL to first-line chemotherapy, the treatment policy is dependent on the age and general condition of the patient. Younger patients in a good condition who showed sensitivity to chemotherapy will be offered high-dose chemotherapy. This will be followed by the reinfusion of their own previously harvested stem cells as rescue therapy, a treatment policy that was shown to be superior to conventional second-line chemotherapy in 1995[15]. For patients who did not show sensitivity to chemotherapy, no standard treatment exists, and the prognosis is usually fatal. Elderly patients will be offered second-line chemotherapy. There is no agreement on the second-line chemotherapy to be applied in these patients.

Many NHL patients are offered treatment in a randomised clinical trial (RCT), in which the standard treatment is compared to a possibly superior alternative. In the Netherlands, the Dutch Working Group on Adult Haemato-Oncology (HOVON) is a very active group in this respect. Since its foundation in 1985, it has ensured the possibility to include patients with haematological malignancies in one of its RCTs.

Central questions of this thesis

The thesis focuses on the economics of diagnosis, treatment and follow-up (including second-line treatments) of aggressive NHL in the Netherlands. The aim was to adequately estimate the actual cost levels of all activities in the course of the treatment of patients (diagnosis, first-line treatment, follow-up, second-line treatment). Because many randomised clinical trials (RCTs) are performed for haematological malignancies and little information on costs and outcomes outside controlled settings is available, the difference between RCT and 'standard local practice' (SLP), also referred to as the difference between efficacy and effectiveness, will be considered as well. This may contribute to the understanding of differences in terms of both costs and outcomes and may facilitate the extrapolation of results from controlled experiments to daily practice.

The following research questions are studied:

1. What is the current situation with regard to diagnosis, treatment, and follow-up of patients with aggressive NHL? What is the rate of RCT participation and which factors might hinder RCT participation?
2. On the basis of the first question: what are the costs of the initial diagnostic phase (the phase during which the patient is newly diagnosed with NHL), costs of the standard first-line treatment and variants thereof, and costs of 1-year of disease-free follow-up, all with a distinction between RCT and SLP?
3. What is the optimal second-line treatment for younger chemotherapy-sensitive aggressive NHL patients who relapsed after or were refractory to first-line chemotherapy? This question will be studied in an RCT context.
4. What is the most cost-effective way of administering the second-line treatment mentioned at the third research question? What are the costs of this second-line treatment and the consequent follow-up? How is the quality of life of these patients and how does this relate to the quality of life of other cancer patients?
5. Are the results obtained in RCTs with the standard first-line treatment during the past 25 years comparable to each other? Is it reasonable to assume that these RCT results are representative of the results obtained in daily clinical practice?
6. Does the overall survival of patients with aggressive NHL differ according to RCT treatment or SLP treatment and if so, to what extent?
7. Can cost-effectiveness results obtained in an RCT in patients with aggressive NHL be representative of cost-effectiveness as obtained in SLP and can underlying causes for divergent costs or effects be identified? Matching for disease specific characteristics will be realised in order to produce unbiased results.
8. Prognostic factors for the survival of patients with aggressive NHL have been determined more than 10 years ago. Can prognostic factors be identified that are able to distinguish groups of

aggressive NHL patients according to their cost profiles and if so, what are these prognostic factors?

9. What is the current state of affairs regarding economic evaluations in NHL and which methodological requirements should (have) be(en) met by these and future economic evaluations?

A framework for the comparison of RCT to SLP

It has been recognised before that differences between efficacy (an intervention's effectiveness under ideal circumstances) and effectiveness (an intervention's effectiveness in daily clinical practice) may occur. Five types of bottlenecks in the care process that might be responsible for differences between efficacy and effectiveness were recognised[16], on the basis of a model of Tugwell and colleagues[17]: 1) the time (between first symptoms and the time) the patient contacts a health care professional, 2) adequate (and timely) diagnosis of the patient's disease, 3) indications for a health care intervention (the extent to which patients receive efficacious health care interventions), 4) adequate realisation of the health care intervention (for example administering it according to recommended doses), and 5) compliance of the patient with the therapy. With regard to the RCT versus SLP question, this thesis focuses on the second, third and fourth of these bottlenecks. The first item is outside the perspective of this thesis and will therefore not be considered, whereas the fifth item does not play a major role in this area, as will be argued later.

Outline of the thesis

Chapter 2 gives an overview of the situation with regard to diagnosis and treatment of NHL in the Netherlands. Beyond the geographical division of the Netherlands in 12 provinces, oncologists have split our country up into 9 'cancer regions'. In every region, a Regional Cancer Centre (RCC) is active in coordinating cancer care. All RCCs have issued their own guidelines on diagnosis and treatment of malignancies, and therefore also of NHL. In the study presented in Chapter 2, an inventory of all current RCC guidelines was made and the contents, including all similarities and differences, will be presented. Also, clinical trials in which these patients can be included are mentioned. In addition, this study included a survey that was sent to a sample of Dutch haematologists, in which they were asked for the diagnostic and therapeutic modalities they applied for NHL in daily clinical practice. The correspondence of the daily practice situation with the RCC guidelines will be presented, as well as the differences. It will also be shown in which clinical trials the haematologists participate and why there may be difficulties in trial participation. The importance of the results for the individual patient and for the development of future national guidelines on diagnosis and treatment of NHL will be emphasised.

In the study presented in Chapter 3, costs of diagnosis, first-line treatment and 1 year of follow-up of patients with aggressive NHL were calculated. With regard to treatment, a few groups were distinguished, according to the most prevailing treatment regimens, as occuring from the survey presented in Chapter 2. As many NHL patients in the Netherlands are treated in clinical trials, a further distinction was made to trial treatments and to treatment according to standard local practice (SLP). The study therefore gives a first insight of the economic effects of including patients in clinical trials. Because the study was based on only small patient groups, no tests of significance were performed, but it provides basic information about the costs of first-line standard chemotherapy for patients with newly diagnosed aggressive NHL and the plausible ranges in which the costs may vary. Beyond the scope of this cost analysis, later chapters will focus on (differences in) effects of trial participation vs. SLP and on a combination of cost and effects.

After having presented the costs of first-line treatment for aggressive NHL in Chapter 3, Chapters 4 and 5 will focus on the costs of the standard second-line treatment for younger patients. Both chapters are based on the results of a Dutch multicenter clinical trial comparing autologous bone marrow transplantation to peripheral blood stem cell transplantation. Chapter 4 will show the details of the clinical results of this trial and a summary of the quality-of-life analysis and the cost analysis that were conducted alongside this trial. Chapter 5 will present the results of these latter two analyses more thoroughly. With regard to the costs, detailed tables will be presented on the costs of the different phases that can be distinguished within this treatment regimen: induction chemotherapy, stem cell harvesting, stem cell reinfusion hospitalisation and 3 months of follow-up. Quality-of-life measures of which the results are shown, are the generic EuroQol and SF-36 questionnaires, and the cancer specific Rotterdam Symptom Checklist. Furthermore, the scores of this patient group on the SF-36 measurement will be compared with the scores of other groups of cancer patients.

As indicated, the earlier chapters in this thesis have partly relied on the results of randomised clinical trials (RCTs). It is however often questioned whether the results of RCTs may be considered to be representative of and therefore generalisable to daily clinical practice. RCT participants often have to meet inclusion criteria, implying that the patients with the worst conditions are left out of consideration. It has been hypothesised that the possibility to generalise results from RCTs is favoured by consistency between the outcomes of these trials. CHOP has been the standard first-line chemotherapy for aggressive NHL ever since 1976, and this treatment has therefore served as the standard comparator to newer treatment alternatives in many RCTs. In a literature review, we tested the hypothesis mentioned above and analysed if the results obtained with standard CHOP in RCTs which have been performed during the past 25 years show consistency. This literature review, from which a theoretical conclusion on the generalisability of RCT results in aggressive NHL can be drawn and which yielded important directions for later practical generalisation studies presented in this thesis, is presented in Chapter 6.

In Chapter 7, the representativeness of RCT treated aggressive NHL patients for their 'daily practice counterparts' was further investigated in terms of overall survival. This study compared patients

included in the most important Dutch RCTs performed in the late 1990's to similar patients who received standard CHOP chemotherapy during this same period according to routine clinical practice in one specific hospital. Together with the earlier study on costs of RCT vs. SLP treatment (Chapter 3), this study can be considered as a pilot study for the larger scale cost-effectiveness study presented in Chapter 8. As such, both studies indicated important practical issues to be considered in this larger scale study.

Chapter 8 presents the results of this study, in which costs and effects of 374 patients with aggressive NHL, either treated in a RCT or according to SLP, were compared. Efficacy (results obtained in selected patients under ideal circumstances) versus effectiveness (results obtained in daily clinical practice) therefore was the central theme of this study. Clues as obtained by the studies presented in Chapters 3, 6 and 7 were taken into account. For economic evaluations of NHL, the patient sample of this study was relatively large, which allowed for additional analyses on subgroups of patients. Beyond base-case analyses, matched pairs analyses (case control studies) on both costs and survival were performed in order to analyse the pure trial effect as much as possible, thereby diminishing the effect of possible confounders.

As stated above, a dataset of 374 patients containing all original specific details on patient characteristics, treatment characteristics and medical resource use, is relatively large for an economic evaluation in NHL. Therefore, Chapter 9 presents a study in which these data were used to investigate if patient characteristics in aggressive NHL might be predictive of total treatment costs. The importance of this question is indicated by the introduction of new pharmaceuticals for NHL, which usually are relatively expensive. Health care decision makers are confronted with limited financial resources on the one hand, and high costs of potentially efficacious new pharmaceuticals on the other. It might therefore be beneficial if subgroups of patients can be identified at forehand, in which new pharmaceuticals are expected to lead to the largest cost-effectiveness gains. Aggressive NHL patients have been distinguished successfully according to effect (survival) since 1993 by the International Prognostic Index for Aggressive NHL (IPI). In this study, it was investigated if this system and an additional variable describing the presence or absence of NHL related symptoms can be used to distinguish subgroups of patients with (un)favourable cost profiles. Costs were calculated up to a maximum of two years after the start of the first-line treatment, and therefore, costs of second-line treatments were also included. Costs of peripheral blood stem cell transplantations, which were presented detailedly in Chapters 4 and 5, were used in this study as a cut-and-dried component.

Chapter 10 finally presents a review of the current available economic evaluations of NHL, next to the analyses presented in this thesis. It groups the available publications into the different topics that have been studied and it shortly describes the current state of affairs with regard to these topics. A second aim of this review was to judge the published economic evaluations on the basis of their methodological merits, because economic evaluations often differ from each other, which is due to different costing methodologies applied. A recent study on costing methodologies, in which 6

methodological issues were identified, was used as the framework for this review. Of all publications included in the review, these 6 issues were identified and will be presented in an overview table.

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Chapter 2. Diagnosis and treatment of non-Hodgkin's lymphoma in the Netherlands; diversity in guidelines and in practice

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Abstract

Objective. To investigate current guidelines for diagnosis and treatment of intermediate or high-grade non-Hodgkin's lymphoma (NHL), stage I-IV (Burkitt's and lymphoblastic lymphoma excluded) and to compare this with current clinical practice.

Design. Descriptive.

Method. An inventory of guidelines for diagnosis and treatment of NHL of the Regional Cancer Centres (RCCs) was made in mid-1998, an enquiry containing questions about the practical situation concerning the diagnosis and treatment of NHL patients was sent to 59 internists-haematologists in non-university hospitals of the RCC regions Amsterdam, Rotterdam, and South.

Results. Apart from the standard diagnostics, the RCCs recommended several examinations for staging. For the initial staging the haematologists did not always request the recommended CTs of chest and abdomen and most of them did no restaging after the last cycle of chemotherapy. Half of them left the assessment of lymph node biopsy samples to a lymphoma panel. The recommended primary treatment consisted mainly of chemotherapy with cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP). In certain regions, the schedule was slightly changed, with additional teniposide and bleomycin (CHVmP/BV). The treatment schedules were heterogeneous, especially for stage I NHL. In leukopenia and/or thrombocytopenia, postponement was recommended, but dosage reduction was carried out immediately, especially in older patients, sometimes with administration of a haematopoietic growth factor. Recurrent NHL was treated in accordance with the guidelines with second-line chemotherapy, if possible followed by peripheral stem cell transplantation in a haemato-oncological centre.

Conclusion. Considering these results, development of national guidelines for NHL would seem to be desirable.

Introduction

To promote efficient health care, the Dutch Ministry of Public Health, Welfare, and Sport (VWS) stimulates the development of clinical practice guidelines on the basis of cost-effectiveness analyses[1]. In order to achieve this, the Institute for Medical Technology Assessment from the Erasmus University Rotterdam conducted a research program[2]. In haemato-oncology, this program started with intermediate and high-grade non-Hodgkin's lymphomas (NHL), stage I-IV (except for lymphoblastic or Burkitt's lymphomas)[3], because of its relatively high incidence. For this disease, study protocols from the Dutch Working Group on Adult Haemato-Oncology (HOVON) and from the European Organization for Research and Treatment of Cancer (EORTC) exist, which have been integrated in trial guidebooks by the Dutch Regional Cancer Centres (RCCs). Moreover, the RCCs issued guidelines, which generally coincide with guidelines from the regional haemato-oncological centres. It is not known to what extent the study protocols and guidelines have been adapted to each other and to what extent they are applied in daily clinical practice. The aim of guideline development is to summarise current scientific knowledge, clinical experience and prevailing expert opinions[4]. We studied the current guidelines for diagnosis and treatment of NHL patients, and analysed the situation in daily clinical practice by means of a survey.

Methods

In mid-1998, all RCCs were asked for their guidelines on NHL and for all prevailing HOVON and EORTC protocols.

Consequently, a survey was designed in order to map the situation in daily clinical practice with regard to diagnosis and treatment of NHL patients. At the end of 1998, this survey was sent to a random sample of 55 internists who were involved in haematology (hereafter referred to as haematologists) in local hospitals from the RCC regions Amsterdam, Rotterdam, and South. The survey was also sent to 4 haematologists outside these regions, who were participating in the consequent part of this project. Returned surveys were analysed by using the statistical software package SPSS[5].

Results

General

The actual guidelines for NHL were obtained from the most recent guideline books from the RCCs Amsterdam (IKA 1987), East (IKO 1997), Rotterdam (IKR 1995), North (IKN 1998), Mid-Netherlands (IKMN 1996), and Limburg (IKL 1996). The RCC West (IKW) referred to the haematology binder of the Leiden University Medical Centre (LUMC 1995); a new version of this binder was issued in June 1999.

The RCC South (IKZ) applied guidelines from the RCCs East, Rotterdam, and Limburg. The RCC City-Triangle Twente applied the RCC Amsterdam guidelines.
Forty-seven of the 59 surveys (80%) were returned from the RCC regions Amsterdam (17), Rotterdam (17), South (9), West (3), and Mid-Netherlands (1). On average, 8.1 (range 2-20) new NHL patients per hospital were seen annually. RCC guidelines were used by 19 (40%) haematologists, guidelines from the neighbouring haemato-oncological centre were used by 23 haematologists (49%), and HOVON or EORTC protocols by 20 (43%) of them. Survey respondents were allowed to give more than one answer to each question.

Diagnosis

The diagnosis at initial staging recommended by all RCCs comprised laboratory diagnostics (sedimentation rate, leukocyte differentiation, liver enzymes including lactate dehydrogenase (LDH), creatinine, serum electrolytes, and immuno-electrophoresis), lymph node biopsy, bone marrow biopsy, chest X-ray, chest CT (RCCs Amsterdam and West recommended this 'on indication'), and an abdominal CT. According to the survey, all haematologists performed the laboratory diagnostics and the lymph node biopsy in daily clinical practice. Almost all haematologists asked for a chest X-ray (41; 87%), an abdominal CT (45; 96%), and a bone marrow biopsy (44; 94%).
Bone marrow aspiration (recommended by RCCs Amsterdam, East, Rotterdam, North, and West), and lymph node cytology (RCCs North and West) were performed by 42 (89%), and 23 (49%) haematologists, respectively. Both the bone marrow aspiration and the bone marrow biopsies were examined locally (39; 83%). Seven (15%) haematologists had their bone marrow aspirations assessed by a lymphoma panel, and 15 (32%) haematologists did so with regard to bone marrow biopsies. Fourteen (30%, aspiration) and 16 (34%, biopsy) haematologists, respectively, had their samples assessed by the regional haemato-oncological centre. Lymph node biopsies (39; 83%) and lymph node puncture (31; 66%) were primarily examined locally. Twenty-five (53%) haematologists had their lymph node biopsies examined by a lymphoma panel, and 9 (19%) did so with regard to lymph node punctures. Eighteen (38%), and 10 (21%) haematologists, respectively, had their samples examined by the regional haemato-oncological centre. Forty-two (89%) haematologists used the Revised European-American Lymphoma (REAL) classification for the histological examination[6, 7]. None of the haematologists regularly performed the direct Coombs' test (recommended by RCCs Rotterdam and Limburg, recommended on indication by RCCs East and North), cold agglutinin test and serum cryoglobulin (advised by RCC Rotterdam, and by RCC North on indication).
Immunophenotyping (recommended by RCCs Amsterdam, Rotterdam, and North; recommended on indication by RCCs East, Mid-Netherlands, West, and Limburg) was performed by 31 haematologists (66%). Cytogenetic tests (recommended by RCC Rotterdam) was done on indication (in trials or in case of uncertainty regarding diagnosis). The same applied for lumbar puncture, which was recommended by most of the RCCs on indication. Ultrasound of the neck (recommended by RCC Rotterdam) and abdomen (recommended by RCCs North and Mid-Netherlands, and by RCC East on

indication) was performed by none of the haematologists in daily clinical practice. Recommended on indication were: CT neck (RCC North), cerebral CT (RCCs Mid-Netherlands, West, and Limburg), cerebral MRI (RCCs North and Limburg), skeletal X-ray (RCCs Rotterdam and West), and an isotope scan (RCCs East, Rotterdam, North, West, and Limburg). The RCCs North and East recommended serological diagnostics (toxoplasmosis, Epstein-Barr virus, cytomegalovirus, Treponema Pallidum Particle Agglutination, HIV, human T-cell lymphotrope virus type I) for differential diagnostics. The RCC Rotterdam recommended virus serology (hepatitis A, B, C, herpes, HIV), cytology and immunology of punctures (blood, liquor, pleural liquid, etc.) and histology of extranodal lesions. The RCC West recommended documentation of the WHO performance status. All RCCs, except for the RCCs East and Rotterdam, recommended a liver biopsy on indication. Other tests recommended on indication were: lung biopsy (RCC Limburg), gastroscopy (RCCs Amsterdam, East, and North), fertility diagnostics and semen preservation (RCCs West and Rotterdam), and a visit to the radiotherapist (RCCs East, Limburg, and Rotterdam). A visit to the otorhinolaryngologist, recommended by almost all RCCs, was regularly required by 35 (75%) haematologists.

Treatment phase

Therapy. For stage I, the RCC guidelines recommended 4x CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with involved field (IF) radiotherapy (RCCs Rotterdam and Mid-Netherlands), 3x CHOP with IF-radiotherapy (RCCs North and Limburg), 3x CHVmP/BV (cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine) with IF-radiotherapy (RCCs East and West), and 6x CHOP followed by IF-radiotherapy if necessary or radiotherapy only (RCC Amsterdam). Radiotherapy doses varied from 30 Gy (RCCs North and West; RCC Limburg in case of complete remission) to 40 Gy (RCCs Mid-Netherlands and East; IKL in case of partial remission).

In practice, treatments varied, depending on malignancy grade, stage and age. Treatment schemes for patients ≤65 years with stage I intermediate grade NHL consisted of 4x CHOP with IF-radiotherapy (15; 32%), 3x CHOP with IF-radiotherapy (13; 28%), 6x CHOP (9; 19%), radiotherapy only (9; 19%), 3x CHVmP/BV with IF-radiotherapy (2; 4%), and 8x CHOP (1; 2%). For stage I high grade NHL, comparable schemes were applied. One haematologist (2%) participated in the EORTC-20901 trial (CHVmP/BV with or without autologous bone marrow transplantation in patients <60 years, closed for inclusion 26 October 1998). Treatment schemes for patients >65 years with stage I were similar, although 6x CHOP and radiotherapy only were applied more often in these patients, whereas 3x CHOP with IF-radiotherapy was applied less often. Radiotherapy doses were hardly mentioned by the survey respondents.

For stage II-IV, the RCC guidelines recommended 6-8x CHOP with or without 'iceberg irradiation' (RCCs Amsterdam, Rotterdam, North, Mid-Netherlands, and Limburg) or 6-8x CHVmP/BV with or without iceberg irradiation (RCCs East and West). Iceberg irradiation is consolidation radiotherapy applied after chemotherapy on initially bulky tumour localisations and/or localisations detectable after 3 chemotherapy cycles. Other recommended therapy schemes were: CHOP with or without

granulocyte colony-stimulating factor (G-CSF) (HOVON-25 trial; ≥65 years); intensive CHOP with G-CSF versus CHOP (HOVON-26; <65 years); triple high-dose chemotherapy plus autologous stem cell transplantation (HOVON-27; ≤65 years, high-risk NHL, from February 1999 onwards for Burkitt's NHL and lymphoblastic NHL only); 3x intensive CHOP followed by HOVON-27 (HOVON-40; ≤65 years, high-risk NHL, excluding Burkitt's NHL, lymphoblastic NHL and mantle cell lymphomas, started in February 1999) (HOVON-25, -26, -27, -40 participation recommended by RCCs Rotterdam, Limburg, Mid-Netherlands, and West); CHVmP/BV with or without radiotherapy (EORTC-20932; >50 years, closed 1 December 1996); CHOP (RCC Limburg), and CHOP with G-CSF (RCC Limburg study; ≥60 years).

In practice, patients ≤65 years were treated with 4x CHOP and IF-radiotherapy (25; 53%), 6x CHOP (14; 29%), 8x CHVmP/BV (1; 2%), or according to HOVON-26 (31; 64%), HOVON-27 (17; 36%), EORTC-20901 (3; 7%). For patients >65 years treatment consisted of 6x CHOP (18; 39%), 8x CHOP (18; 39%), 8x CHVmP/BV (1; 2%) or the HOVON-25 trial (26; 55%) or EORTC-20932 trial (2; 5%). In case of 'bulky disease', the majority (39; 82%) applied radiotherapy (IF-radiotherapy or iceberg irradiation) after chemotherapy. Bulky disease implies a tumour localisation with a diameter ≥ 10 cm and/or a mediastinal bulk larger than one third of the internal transversal thoracic diameter on level TV/VI. All treatments were primarily administered on an outpatient basis.

Consultation. For their treatment choice, fifteen (31%) haematologists used the prognostic factors of the HOVON, which are virtually the same as the factors of the 'International Prognostic Index' that are also applied in the Netherlands[8].

Thirty-four (73%) haematologists discussed all their new NHL patients during specific haemato-oncological meetings; 13 (27%) haematologists only discussed their 'problem cases'. Additionally, 37 (78%) haematologists had frequent telephone discussions with the RCC consultant or the haemato-oncological centre. Almost all 47 of these haematologists were satisfied with this consultation situation. The consultant's recommendation was followed by 32 (68%) haematologists in all cases. Reasons for not following the recommendations were conflicts with one's own opinion, an advice that was not suited to the patient in question, or a consultant who was not a haematologist.

Dose modification of chemotherapy. RCCs Amsterdam, North, East, and West recommended dose modification for CHOP cycles in case of leukocytopenia and/or thrombocytopenia. In case of a leukocyte count of $<4x10^9$/l and/or a thrombocyte count of $<100x10^9$/l, a one week delay in administering the chemotherapy cycle was recommended. Consequently, 50% dose reduction (RCC Amsterdam: 75%) of doxorubicin and cyclophosphamide was recommended in case of a leukocyte count of $2\text{-}3x10^9$/l and/or a thrombocyte count of $50\text{-}100x10^9$/l. The RCC Amsterdam recommended 50% dose reduction in case of a leukocyte count of $3\text{-}4x10^9$/l and/or a thrombocyte count of $50\text{-}100x10^9$/l as well as cycle delay in case of a leukocyte count of $<2x10^9$/l and/or a thrombocyte count of $<50x10^9$/l. The RCC East recommended 25% dose reduction in case of a leukocyte count of $3\text{-}4x10^9$/l and/or a thrombocyte count of $\geq 100x10^9$/l. In case of neurotoxicity, it was recommended to halve the vincristine dose (RCCs East and West). For CHVmP/BV cycles, similar recommendations applied to

the doxorubicin, cyclophosphamide, and teniposide doses (RCCs Amsterdam, East, and West). In case of bone marrow involvement, it was not recommended to modify doses.
In case of leukopenia ($<3x10^9/l$) and/or thrombocytopenia ($<100x10^9/l$), 35 (75%) haematologists delayed the cycle administration by one week; 8 of them (18%) immediately modified doses of the chemotherapy, and 14 (30%) administered G-CSF at following cycles. G-CSF administration was primarily applied in elderly patients (23; 49%).

Response evaluation and follow-up
For evaluation of response, almost all RCCs recommended restaging after the third cycle and after the sixth and/or eighth cycle or after consolidation radiotherapy. The majority of the haematologists (37; 79%) performed restaging after the third cycle; the others did so after the second or fourth cycle; 12 (26%) also performed restaging after the sixth and/or eighth cycle. After the treatment, follow-up visits were done at 2-3 months intervals (in the first year) and at 3-4 month intervals (after the first year), which is comparable to the RCC recommendations.

Relapsed / refractory NHL
In case of relapsed or refractory NHL, all haematologists discussed the treatment options with the regional haemato-oncological centre. For the younger patients, the general RCC recommendation was high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation. Treatment schemes applied were: 3x ProMACE-CytaBOM (cyclophosphamide, etoposide, prednisone, cytarabine, vincristine, bleomycin, methotrexate, leucovorin) followed by BEAM (carmustine, etoposide, cytarabine, melphalan) with peripheral blood stem cell transplantation (RCC East), DHAP (dexamethasone, cytarabine, cisplatin) followed by BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) with peripheral blood stem cell transplantation (RCC Rotterdam), DHAP-VIM-(etoposide, ifosfamide, mesna, methotrexate)-DHAP followed by BEAM with peripheral blood stem cell transplantation (RCC West), or DHAP-VIM-DHAP followed by BEAM with peripheral blood stem cell transplantation versus BEAM with autologous bone marrow transplantation (HOVON-22 trial; $\leq$65 years, closed for inclusion 30 September 1998) (RCCs Mid-Netherlands and West). Besides this, the RCC Rotterdam recommended allogeneic bone marrow transplantation for patients <55 years and >20% lymphoma involvement within the bone marrow. The RCC East recommended 6-8x ProMACE-CytaBOM with or without radiotherapy for patients >60 years. The surveyed haematologists (19; 40%) treated younger patients with second-line chemotherapy (for example IMVP (ifosfamide, mesna, etoposide, methotrexate) or DHAP), if possible followed by high-dose chemotherapy with peripheral blood stem cell transplantation in a haemato-oncological centre. The other second-line therapy recommended by the RCCs consisted of chemotherapy (RCC North), for example ProMACE-MOPP (prednisone, methotrexate, leucovorin, doxurubicin, cyclophosphamide, etoposide, mitoxine, vincristine, procarbazine) (RCCs Amsterdam and Mid-Netherlands), IMVP (RCC Amsterdam), CEPP (lomustine, etoposide, chlorambucil, prednisone) (RCC East), DHAP (RCC Rotterdam), etoposide +

cyclophosphamide (RCC Mid-Netherlands), CEP (chlorambucil, etoposide, prednisone) (RCC Mid-Netherlands), MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) (RCC West), gen therapy (RCC Rotterdam), and/or radiotherapy (RCCs East and North).

Treatment obstacles

Haematologists considered the treatment of relapsed / refractory NHL (10; 21%) and multidisciplinary logistic problems (11; 23%) as difficulties regarding treatment. With regard to relapsed / refractory NHL, adequate treatment of elderly patients and support of patients during end-stage disease were considered to be difficult.

Discussion

At the request of the Minister of Public Health, Welfare, and Sport (VWS), an inventory of current guidelines for intermediate and high-grade NHL was made. With regard to diagnosis and treatment of NHL, both consistencies as well as inconsistencies between the RCC guidelines themselves and between the RCC guidelines and the situation in practice were observed. Only a small percentage of lymph node biopsies and bone marrow biopsies was examined by a lymphoma panel. It is not known if this was caused by pathologists, who sent the samples to a lymphoma panel. Moreover, at initial staging, abdominal and thoracic CT scans were not always made when they should have been made, and restaging after the last chemotherapy cycle was only done by a small number of haematologists[9].
The standard treatment CHOP or CHVmP/BV was recommended by the majority of the RCCs, and was applied in practice by most of the haematologists[10-12]. Following recent literature, a limited number of CHOP(-like) chemotherapy cycles followed by radiotherapy were recommended for stage I, however the treatment schemes applied were heterogeneous[13]. Treatment in trials was a main issue for most of the RCCs. Eighty-five percent of the surveyed haematologists participated in HOVON and EORTC trials, mainly because of the quality enhancing effect. However, in practice, trial participation is considered to be only modest (source: HOVON trial centre). Reasons for not participating were a lack of time and logistic problems. The establishment of a general ethical procedure might circumvent this problem.
In practice, chemotherapy doses were reduced in case of leukocytopenia or thrombocytopenia. Several prospective studies have shown dose reduction of CHOP to lead to significantly worse treatment results in elderly NHL patients, as compared to standard doses[14-17]. Supportive therapy with haematopoietic growth factors might be considered, but this is not an established indication yet.
This inventory yielded important data for the development of future guidelines of NHL. The next step of this project is a cost-effectiveness analysis, the results of which will be used in the definition of the NHL guidelines, in cooperation with other clinicians and representatives of the RCCs.

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Chapter 3. Cost analysis of CHOP (-like) chemotherapy regimens for patients with newly diagnosed aggressive non-Hodgkin's lymphoma

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Abstract

Many cost analyses of stem cell transplantations are available, which is in sharp contrast to the level of cost analyses on first-line chemotherapy for aggressive non-Hodgkin's lymphoma (NHL). Given the scarcity of cost analyses of first-line chemotherapy for NHL, it is difficult to assess the economic impact of upcoming new treatment modalities. Therefore we performed an analysis on costs of diagnosis and treatment of patients with newly diagnosed NHL who were treated with standard CHOP (-like) chemotherapy. As many NHL patients are treated in trials and the economic effects of the trial participation are unknown, our analysis included both patients treated according to trial protocols and patients treated according to standard local practice (SLP). The cost analysis was based on the total medical consumption of the patients. It was found that costs of the trial and SLP groups are within comparable ranges, although costs of diagnostic tests were somewhat higher within the trials. In elderly patients, SLP chemotherapy was discontinued more frequently in case of leucocytopenia or thrombocytopenia. This analysis provides basic information about the costs of first-line standard chemotherapy for patients with newly diagnosed aggressive NHL and the plausible ranges in which these costs may vary. Given the results, we will initiate larger studies to investigate whether trial treatments (showing more or less similar costs as SLP treatments) are more cost-effective for patients with aggressive NHL.

Introduction

A considerable amount of literature has been published on the economics of bone marrow or peripheral blood-derived stem cell transplantation for second-line treatment of lymphomas. However, only limited experience with cost analyses has been established on first-line standard chemotherapy for aggressive NHL, in a well defined group of patients[1]. Since the mid-1970's, the standard chemotherapy regimen for first-line treatment of NHL has been CHOP (-like) treatment. Several third-line chemotherapy schemes have so far not significantly improved remission or survival rates[2-7]. Given the scarcity of cost analyses of first-line chemotherapy for NHL, it is difficult to assess the economic impact of these and upcoming new treatment modalities.

Although many NHL patients are included in clinical trials, a significant proportion of these patients are treated by haematologists outside the context of a clinical trial according to locally adopted guidelines. It has been shown that trial treatments are not necessarily more expensive[8, 9]. On the other hand, the performance of diagnostic procedures subject to strict protocols might lead to higher costs. Furthermore, the setting in which care is provided (e.g. university vs. local hospital, inpatient vs. outpatient) exerts an important influence on the costs of treatment[10, 11]. Trial treatments are often administered in university hospitals, whereas non-trial first-line treatment of NHL is frequently applied in local hospitals. The magnitude of these possible cost effects of trial treatments is still unknown.

In order to gain an insight into the costs of standard first-line therapy of patients with NHL, we performed a cost analysis on the most prevailing first-line standard treatments for adults with newly diagnosed aggressive NHL, focusing on differences between patients who were treated according to trial protocols and comparable patients who were diagnosed and treated according to standard local practice.

Patients and methods

In 11 Dutch local hospitals a random selection was made of patients with intermediate or high-grade non-Hodgkin's lymphoma according to the Working Formulation[12], and Ann-Arbor stage II-IV[13]. Burkitt's and lymphoblastic lymphomas were excluded. A distinction was made between younger (<65 years) and elderly (≥65 years) patients, according to the distinction of the Dutch Working Party on Haemato-Oncology ('HOVON'). These patients were treated with CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) or CHOP-like chemotherapy CHVmP/BV (cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine). The selection procedure consisted of a random draw of patient registration numbers from hospital lists. No further selection criteria were applied beforehand, as matching of patients according to age, gender or prognostic criteria was not an aim in this analysis.

The younger patients were randomly selected from the following groups:

PROT1-yng: Treatment according to the NHL-26 protocol of the Dutch Working Party on Haemato-Oncology ('HOVON'), which randomised patients to 8 x CHOP q 3 weeks or 6 x CHOP q 2 weeks + recombinant Human Granulocyte Colony Stimulating Growth Factor (rG-CSF, Neupogen®).
PROT2-yng: Eight cycles of the CHOP-like CHVmP/BV regimen (q 3 weeks, CHVmP administered on day 1, BV on day 15) administered according to the guidelines of the European Organization for Research and Treatment of Cancer 20.90.1 protocol[14].
SLP-yng: Patients who would have been eligible for trial inclusion, but nevertheless received 6 x or 8 x standard CHOP q 3 weeks according to local practice, i.e. not within the context of a trial.
Elderly patients were randomly selected from the following two groups:
PROT-eld: Treatment according to the HOVON NHL-25 protocol, which randomised patients to 6 x or 8 x (depending on response) CHOP q 3 weeks ± rG-CSF[15].
SLP-eld: Patients who received 6 x or 8 x standard CHOP q 3 weeks according to local practice, i.e. not within the context of a trial. Just as the younger patients, these patients would have been eligible for trial inclusion.
This study was designed to give basic information of the costs within these groups and not to demonstrate significant differences between them. Therefore, we aimed to include 25 patients in each group, which we considered to be a sufficient number for the analysis, within the given time frame.
In all groups, three periods were assessed: 'diagnosis' (first visit to haematologist until the day before start of chemotherapy), 'treatment' (start date of chemotherapy until 10 days after administration of final cycle), 'follow-up' (day after stop date of treatment phase until 1 year after the end of treatment, or -if earlier- death). If a recurrent NHL was observed within 1 year, the follow-up phase was censored at the date the diagnosis recurrent NHL was confirmed, as the aim of this analysis was only to consider costs belonging to the first-line treatment. Follow-up was not assessed at all if the patient was resistant to the first line treatment or if he or she died within the treatment phase. In this way, only 'disease-free follow-up' has been taken into account.
Within these three phases, the total medical consumption of the patients was assessed. Average unit costs were determined for the most important items within the medical consumption, reflecting full hospital costs, including overhead costs[16, 17]. To determine these unit costs (Table 1), we followed the micro-costing method. This method is based on a detailed inventory and measurement of resources consumed, e.g. materials and disposables used and time spent by nursing staff[18]. The valuation of the resources and overhead costs was based on financial data from five of the participating hospitals (1998 level). Diagnostic tests and other procedures were multiplied by Dutch tariffs, as these are proper approximations of the actual unit costs[17]. Costs of medication were based on Dutch 1998 wholesale prices[19]. The hospital perspective[20] was applied.
Statistical analyses were performed using SPSS for Windows, version 10.0. A 5% two-sided significance level was applied. The chi-square test was applied to compare patient characteristics. As none of the variables was distributed normally, comparisons of two groups were performed using the Mann-Whitney U-test. Comparisons of more than two groups were performed applying the Kruskal-

Wallis H-test. All data are presented as mean values per patient.

Table 1. Unit costs (in Euros) within local hospitals.

Cost component	Haematology hospital day	Haematology outpatient visit	Haematology use of day care centre	RT MV session	Lymph node biopsy under anaesthesia
Specialist	35	27	11	13	53
OR personnel, incl. anaesthesia	-	-	-	-	139
Nursing and administration staff	113	9	41	54	-
Nutrition	12	-	-	-	-
Materials	25	2	21	16	130
Housing and overhead	74	7	44	25	95
Total	**259**	**45**	**117**	**108**	**417**

OR, operation room; RT MV, radiotherapy megavolt. The costs of the daycare centre included fixed costs of the daycare centre personnel and the use of the rooms for administering chemotherapy or blood components (note that costs of cytostatics and the blood components themselves have been calculated separately).

Results

Patients

Characteristics of the 116 NHL patients are presented in Table 2. The patients were diagnosed in 1991 (4), 1992 (5), 1993 (13), 1994 (9), 1995 (30), 1996 (20), 1997 (22), 1998 (8), and 1999 (5). Of the three groups with younger patients, only the age differed significantly. The SLP-yng patients were older than the PROT1-yng patients, and both groups were older than the PROT2-yng patients. There were no age differences between the two elderly patient groups. The SLP-eld group contained more patients with advanced (stage III or IV) lymphomas.

Except for the PROT1-yng group, all groups contained one patient who died during the treatment phase. Follow-up was not assessed for respectively six (PROT1-yng), five (PROT2-yng), four (SLP-yng), and four (PROT-eld) patients, respectively, as they were resistant to first-line treatment, and immediately went on to salvage treatments.

Diagnosis in younger patients

The diagnostic phase lasted 28.71 (PROT1-yng), 30.48 (PROT2-yng), and 26.00 (SLP-yng) days on average (P= ns), and the patients were hospitalised for, respectively, 9.83, 9.54, and 7.17 days (P= ns). During this phase, the patients visited the haematology outpatient clinic 2.61 (PROT1-yng), 3.75 (PROT2-yng), and 2.16 (SLP-yng) times, respectively. Table 3 illustrates the total costs of the diagnostic phase.

Diagnosis in elderly patients

The duration of this phase was similar for both groups: 30.62 (PROT-eld) and 30.95 (SLP-eld). The number of hospital days (14.42 and 8.21, respectively) and the number of outpatient visits (2.95 and 3.12, respectively) were not statistically different. The total costs are shown in Table 4.

Table 2. Patient characteristics.

		Patients <65 years				Patients ≥ 65 years		
		PROT1-yng	PROT2-yng	SLP-yng	P-value	PROT-eld	SLP-eld	P-value
Sample size	n	24	25	24	-	24	19	-
Gender	male	0.50	0.72	0.79	0.081	0.46	0.58	0.432
	female	0.50	0.28	0.21		0.54	0.42	
Age	mean (SD)	49 (10)	40 (11)	56 (7)	0.000	73 (6)	73 (7)	0.941
	median	52	40	58		73	71	
	range	27-64	19-59	39-64		65-87	66-94	
	≤60	0.96	1.00	0.62	0.000	0.00	0.00	1.000
	>60†	0.04	0.00	0.38		1.00	1.00	
Serum LDH level	≤1x normal	0.92	0.67	0.88	0.054	0.83	0.94	0.271
	>1x normal†	0.08	0.33	0.12		0.17	0.06	
ECOG Performance score	Ambulatory	0.96	0.75	0.79	0.122	0.83	0.83	1.000
	Not ~ †	0.04	0.25	0.21		0.17	0.17	
Ann Arbor stage	I or II	0.21	0.40	0.38	0.299	0.08	0.33	0.041
	III or IV†	0.79	0.60	0.62		0.92	0.67	
Extranodal sites	≤1 localisation	0.71	0.76	0.92	0.177	0.62	0.79	0.244
	>1 localisation†	0.29	0.24	0.08		0.38	0.21	
WF Malignancy Grade	intermediate	0.71	0.68	0.83	0.432	0.75	0.74	0.922
	high	0.29	0.32	0.17		0.25	0.26	
Systemic B-symptoms	absent	0.67	0.52	0.44	0.270	0.62	0.61	0.927
	present	0.33	0.48	0.56		0.38	0.39	
Bone marrow infiltration	absent	0.65	0.80	0.87	0.175	0.50	0.79	0.051
	present	0.35	0.20	0.13		0.50	0.21	

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; ambulatory = ECOG score 0 or 1; not Ambulatory = ECOG score 2-4; WF, Working Formulation[12]; LDH, lactodehydrogenase. Systemic B-symptoms were defined as the existence of fever (>38.3°C), night sweating, or an unexplained weight loss of >10% of the original body weight.
† = Significant prognostic factor for a worse treatment result[21].

Treatment in younger patients

The treatment phase (Table 3) lasted 140.54 (PROT1-yng), 147.54 (PROT2-yng), and 149.63 (SLP-yng) days, respectively (ns). On average, 7.08, 6.63, and 6.71 cycles of chemotherapy were administered (ns), respectively. In the trial groups, significantly more cycles were administered in the outpatient clinic. In both trial groups, only 16% of all chemotherapy cycles were administered during hospitalisation, as compared to 38% in the SLP-yng group (P= 0.005). In spite of the higher hospitalisation frequency by the SLP-yng group, the number of hospital days during this phase was not significantly different: 8.75 (PROT1-yng), 12.35 (PROT2-yng), and 15.25 days (SLP-yng). The number of visits to the haematology outpatient clinic differed (3.78, 5.63, and 4.89, respectively). The costs of using the daycare centre were higher in the PROT2-yng group, as a consequence of the subdivision of each chemotherapy cycle in two administrations on day 1 and 15. PROT2-yng patients used the daycare centre 11.43 times on average, as compared to 6.00 (PROT1-yng) and 4.29 (SLP-yng). In the trial groups, costs of diagnostic tests were somewhat higher, due to the fact that according to protocol these tests were done at higher frequency (Table 3). In all groups, about 20% of the total

costs were spent on cytostatics.

Table 3. Mean costs (in Euros) per patient (<65 years) during the diagnostic phase, treatment phase, and follow-up phase.

	Diagnosis			Treatment			Follow-up		
	PROT1-yng	PROT2-yng	SLP-yng	PROT1-yng	PROT2-yng	SLP-yng	PROT1-yng	PROT2-yng	SLP-yng
Hospitalisation	2539	2464	1851	2259	3188	3937	488	1792	1835
Haematology outpatient visits	118	168	97	170	253	220	240	433	264
Other consultations	35	43	35	28	19	26	13	31	12
Day care centre use	-	-	-	708	1348	506	-	-	-
Radiotherapy	-	-	-	0	171	0	335	491	575
Pathology diagnostics	802	754	679	266	414	107	136	142	309
Laboratory diagnostics	181	196	139	406	612	393	183	354	281
Immunology diagnostics	272	136	193	9	0	0	57	0	45
Microbiology diagnostics	64	27	12	83	86	44	3	35	29
Radiology diagnostics	507	566	388	647	741	395	285	556	395
ECG/EEG/EMG	10	12	9	5	18	7	3	10	4
Other diagnostics	146	168	172	111	143	26	64	0	266
Blood components	102	0	0	299	653	72	19	9	0
Cytostatics	-	-	-	2069	2184	1791	-	-	-
rG-CSF	-	-	-	3006	674	863	-	-	-
Antibiotics	40	0	0	152	98	38	0	25	0
Other medication	21	24	0	22	83	50	0	14	0
Total costs	**4837**	**4560**	**3576**	**10239**	**10683**	**8473**	**1825**	**3893**	**4015**
excluding hospital days	2298	2096	1725	7979	7495	4535	1337	2100	2180
excluding rG-CSF	-	-	-	7232	10009	7610	-	-	-
excluding hospital days + rG-CSF	-	-	-	4973	6821	3672	-	-	-

Treatment in elderly patients

The treatment phase lasted longer in the PROT-eld group (146.21 vs. 106.74 days, P= 0.002), due to a higher number of chemotherapy cycles in these patients (6.96 vs. 5.32, P= 0.002). Although the numbers of hospital days showed no differences (14.29 PROT-eld vs. 14.74 SLP-eld), the percentage of chemotherapy cycles administered on an inpatient basis was lower in the PROT-eld group (25% vs. 53%, P= 0.026). Consequently, the costs of using the daycare centre for chemotherapy administration were higher in the PROT-eld group. Table 4 shows that in elderly patients the costs of diagnostic tests were somewhat higher in the trial group, similar to the situation in younger adults. Costs of cytostatics amounted to approximately 16% of the total costs.

Follow-up in younger patients

Only disease-free follow-up was taken into account. Assessment of a complete 1-year disease-free follow-up was possible for 11 (PROT1-yng), 13 (PROT2-yng), and 13 (SLP-yng) patients. The follow-up of the remaining patients was less than 1 year because of death (0, 1, and 3, respectively) or recurrent disease (7, 4, and 3, respectively).

Although the length of follow-up did not show significant differences [249.72 (PROT1-yng), 305.89 (PROT2-yng), and 306.58 days (SLP-yng)], the median values (321, 365, and 365 days, respectively) indicated that the PROT1-yng group contained fewer patients for whom a full year of follow-up could be assessed. The average duration of hospitalisation was 1.89, 6.94, and 7.11 days respectively (P= ns), but these average numbers were mainly constituted by a small number of patients who had been hospitalised during this phase (medians were 0 in all groups). Patients were seen in the outpatient clinic 5.33, 9.65, and 5.87 times, respectively. The costs are presented in Table 3.

Follow-up in elderly patients

A complete 1-year disease-free follow-up was possible for 14 (PROT-eld) and 11 (SLP-eld) patients, because three and two patients died within the first year of follow-up, while two and one patients had a relapse of NHL, respectively. The follow-up durations (284.32 and 309.71, respectively) did not show significant differences. The average number of hospital days was, respectively, 4.42 and 11.57, but again these average numbers were constituted by a small number of hospitalised patients (medians were 0). Relatively more patients in the SLP-eld groups were treated with palliative radiotherapy. Total costs are shown in Table 4.

Table 4. Mean costs (in Euros) per patient (> 65 years) during the diagnostic phase, treatment phase, and follow-up phase.

	Diagnosis		Treatment		Follow-up	
	PROT-eld	SLP-eld	PROT-eld	SLP-eld	PROT-eld	SLP-eld
Hospitalisation	3722	2120	3690	3805	1142	2988
Haematology outpatient visits	133	140	256	166	304	221
Other consultations	16	29	22	18	9	36
Day care centre use	-	-	603	304	-	-
Radiotherapy	-	-	0	6	51	924
Pathology diagnostics	803	648	360	187	284	160
Laboratory diagnostics	201	128	404	295	248	250
Immunology diagnostics	272	244	34	23	30	39
Microbiology diagnostics	46	8	102	49	5	16
Radiology diagnostics	536	433	718	424	457	280
ECG/EEG/EMG	13	10	23	8	13	3
Other diagnostics	239	153	333	56	59	94
Blood components	0	0	122	30	0	0
Cytostatics	-	-	1727	1336	-	-
rG-CSF	-	-	2954	842	-	-
Antibiotics	14	0	229	28	0	0
Other medication	6	0	96	86	21	0
Total costs	**6000**	**3914**	**11673**	**7663**	**2623**	**5010**
excluding hospital days	2278	1794	7983	3858	1482	2022
excluding rG-CSF	-	-	8719	6821	-	-
excluding hospital days + rG-CSF	-	-	5029	3016	-	-

Robustness

To give an impression of the plausible range in which the costs may vary, Table 5 shows the main cost items for each phase with their 95% confidence intervals. The 'other costs' (total costs excluding hospital days and rG-CSF) were the most stable cost category of our analysis, as they only varied within a limited range. The average costs of rG-CSF of this analysis are not representative, because the growth factors were only administered to some of the patients. Hospitalisation costs showed wide variations, since the average costs of all patients were particularly constituted by data from a few patients who were hospitalised relatively long or often. Most patients were hospitalised only a few days (diagnosis, treatment) or were not hospitalised at all (follow-up).

Table 5. Mean costs (in Euros) and 95% confidence intervals of diagnosis, treatment, and follow-up.

	Patients <65 years			*Patients ≥ 65 years*	
	PROT1-yng	PROT2-yng	SLP-yng	PROT-eld	SLP-eld
Diagnosis:					
- Hospitalisation	2539 (1515-3563)	2464 (1340-3588)	1851 (678-3022)	3722 (2036-5410)	2120 (876-3364)
- Other costs	2298 (1923-2674)	2096 (1944-2249)	1725 (1533-1918)	2278 (2153-2402)	1794 (1526-2062)
- Total costs	**4837 (3559-6116)**	**4560 (3352-5769)**	**3576 (2344-4808)**	**6000 (4344-7656)**	**3914 (2518-5310)**
Treatment:					
- Hospitalisation	2259 (1014-3505)	3188 (1655-4721)	3937 (2087-5788)	3690 (1865-5515)	3805 (2018-5592)
- Other costs	4973 (4440-5506)	6821 (6278-7365)	3672 (3300-4045)	5029 (4461-5596)	3016 (2440-3593)
- rG-CSF	3006 (1789-4223)	674 (34-1314)	863 (86-1639)	2954 (1655-4253)	842 (0-1907)
- Total costs	**10239 (7938-12539)**	**10683 (8932-12434)**	**8473 (6239-10706)**	**11673 (9127-14220)**	**7663 (5440-9887)**
Follow-up:					
- Hospitalisation	488 (0-986)	1792 (0-3771)	1835 (67-3602)	1142 (158-2125)	2988 (0-6791)
- Other costs	1337 (804-1870)	2100 (1658-2543)	2180 (1522-2838)	1482 (1153-1881)	2022 (1452-2592)
- Total costs	**1825 (1129-2520)**	**3893 (1766-6018)**	**4015 (1988-6041)**	**2623 (1507-3739)**	**5010 (1356-8664)**

Discussion

We investigated costs of trial regimens and standard local practice (SLP) for diagnosis, treatment, and follow-up of younger and elderly patients with newly diagnosed intermediate or high-grade NHL who were treated with standard chemotherapy. Only CHOP (-like) chemotherapy was included, as this has been the standard first-line treatment for aggressive NHL since the mid-1970's[2-7, 22-25]. It can be concluded that in both younger patients and elderly patients, costs of diagnosis and treatment are within comparable ranges between trial and non-trial patients. Costs of diagnostic tests tend to be somewhat higher in the context of a clinical trial. In the CHVmP/BV scheme, costs of using the daycare treatment centre were higher due to the treatment with bleomycin and vincristine (BV) at mid-cycle. We found that the costs of trial treatment in elderly patients were slightly higher mainly as a result of the higher average number of chemotherapy cycles administered. This is consistent with our previous study that showed that in local practice, chemotherapy doses were reduced sooner or were discontinued more frequently in case of leucocytopenia or thrombocytopenia[25].

Cost analyses are frequently performed in connection to clinical trials, which are often performed in selective hospitals. As costs can differ largely between different types of hospitals[10, 11], cost analyses connected to clinical trials may not be representative of the costs of treatment in other hospitals[26]. Since first-line treatment of NHL is often performed in local hospitals, we have only used patient data and financial data from local hospitals in this analysis. Although we assume that this has enhanced the general representativeness of the analysis, we cannot definitely exclude an implicit artificial cost difference between our trial and non-trial groups due to specific hospital differences. If such differences have been incorporated, the costs of SLP treatments are probably somewhat underestimated in this analysis, while the costs of the trial treatments may have been overestimated.
In general, all CHOP (-like) regimens can be administered on an outpatient basis. The necessity to administer chemotherapy clinically or to hospitalise patients in the case of complications is highly dependent on the condition of the individual patient. However, it may also simply be specific hospital policy to hospitalise patients for chemotherapy administration. The reported average hospitalisation costs in this analysis are therefore only approximations. The reported average rG-CSF costs are also approximations, because only some of the patients were treated with rG-CSF. If rG-CSF support is considered necessary, the costs of the treatment will rise with approximately € 1.150 per cycle.
A limitation of this analysis is the small sample sizes on which it is based. We have tried to reinforce our results by identifying subgroups that may have been responsible for relatively high or low costs. In this context, distinguishing the costs of the follow-up phase between patients who reached a disease-free 1-year follow-up and others who did not yielded additional insights for the young patients. Compared to the original analysis, this particularly implied a difference for the PROT1-yng group that originally contained relatively more patients who were resistant to the first-line treatment or who experienced a recurrent tumour within the first follow-up year. The average total costs excluding hospital days of young patients who reached a disease-free 1-year survival were highly comparable between the three groups [€ 2.199 (PROT1-yng), € 2.133 (PROT2-yng), € 2.158 (SLP-yng)], with similar distributions of the specific cost items.
This analysis provides basic information about the costs of first-line standard chemotherapy for patients with newly diagnosed aggressive NHL and the plausible ranges in which these costs may vary (for information on costs of second-line therapy for this patient group, calculated according to the same methodology, we refer to reference 27). It turned out that the costs of trial treatments and SLP treatments are within comparable ranges, although the costs of diagnostic tests tend to be somewhat higher in the trial regimens. Given the comparable cost ranges, an interesting topic still to be investigated is the potential of trial treatments to be a more cost-effective treatment approach than a SLP treatment. It has already been postulated that trial treatments in cancer lead to better results than non-trial treatments[28]. Although this study does not allow for definite conclusions, it may suggest a higher cost-effectiveness within the trial regimens. Although the diagnostic tests induced slightly higher costs, it could be possible that the initial diagnosis was more accurate and that the trial schemes subject to strict protocols ensured a better monitoring of patients during the treatment as

compared to the SLP groups. Some earlier studies indicate the occurrence of such an incomplete staging in some patients[29, 30]. It has also been recognised that earlier cessation of chemotherapy or dose reduction, which we observed in elderly patients, may lead to worse treatment results[31]. Moreover, savings within the trial regimens may also occur. Our trial patients were, for example, treated on an outpatient basis more frequently than the non-trial patients. Furthermore, it should be kept in mind that costs of a trial treatment are not necessarily higher to hospitals or insurers, as additional costs within sponsored trials are often borne by pharmaceutical companies. Given these considerations, it may very well be that the cost-effectiveness (relation of the costs to the remission and survival rates) of the trial regimens with protocols is better than the cost-effectiveness of the SLP treatments. Large-scale comparisons will be initiated to analyse cost-effectiveness of the trial and non-trial settings in which both economic and clinical outcome measures are recorded in order to calculate costs per life-year gained and to reach definite conclusions on this subject.

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Chapter 4. Autologous peripheral blood stem cell transplantation in patients with relapsed lymphoma results in accelerated haematopoietic reconstitution, improved quality of life and cost reduction compared with bone marrow transplantation: the Hovon 22 study

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Abstract

The present study analysed whether autologous peripheral blood stem cell transplantation (PSCT) improves engraftment, quality of life and cost-effectiveness when compared to autologous bone marrow transplantation (ABMT). Relapsing progressive lymphoma patients (n=204; non-Hodgkin's lymphoma n=166; Hodgkin's disease n=38) were, after induction treatment with the DHAP-VIM (cisplatin, cytarabine, dexamethasone, etoposide, ifosfamide, methotrexate) regimen, randomly (2:1) assigned to the harvest of granulocyte-macrophage colony-stimulating factor-mobilized stem cells after the second DHAP course or autologous bone marrow cells before the second DHAP course. These stem cells were reinfused following high-dose myeloblative chemotherapy. After induction, 118 patients obtained a partial or complete response and were eligible for randomization. In the PSCT arm (n=76) significantly faster engraftments of neutrophils ($\geq$ 0.1 and $\geq$ 0.5 x 10^9/l: 10.7 days (7-36, median, range), 15 (9-45) versus 13 (8-25) and 26 (14-80), P< 0.01) and thrombocytes ($\geq$ 20 x 10^9/l: 13 days (7-51) versus 18 (11-65), P< 0.01) were observed. In addition, significantly fewer transfusions of red blood cells [6 (0-23) versus 8 (2-24), P< 0.01] and platelets [4 (0-60) versus 8 (2-55), P= 0.01] were required in the PSCT arm. These findings were associated with a significant reduction in the median days of intravenous antibiotics in patients with fever [8.5 (0-30) versus 14 (0-34), P= 0.04] and hospital stay [27 (8-51) versus 34 (24-78), P< 0.05]. Quality of life demonstrated a significant difference in favour of the PSCT arm. Total transplantation costs were significant lower in the PSCT arm ($13954 ($4913 - $29532) versus $17668 ($10170 - $44083) P< 0.05), as a result of the reduced hospital stay and lower antibiotic costs.

In summary, these results indicate that PSCT is superior to ABMT with regard to engraftment, supportive care, quality of life and cost.

Introduction

Since the introduction of haematopoietic growth factors, peripheral blood stem cell transplantation (PSCT) has been increasingly applied in the setting of autologous and allogeneic transplantation. This strategy has been followed as most retrospective studies revealed a faster recovery of peripheral blood counts after myeloblative chemotherapy, which coincided with a shorter period spent in the hospital and a decrease in costs[1-3]. To date, a limited number of studies in a small number of patients have prospectively evaluated the value of PSCT compared with autologous bone marrow transplantation (ABMT)[4, 5]. In the study of Schmitz and colleagues[4], granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral stem cells were superior to autologous bone marrow with regard to platelet engraftment and discharge from hospital. The data regarding neutrophil engraftment were flattered by the fact that all patients received G-CSF post-transplantation. In addition, no information was reported regarding the cost-effectiveness of the procedure or improvement in quality of life.

Various chemotherapy regimens have been described for patients with progressive recurrent lymphoma. Extensive experience has been obtained with the DHAP (cisplatin, cytarabine, dexamethasone) regimen prior to myeloblative chemotherapy[6, 7]. Around 40-60% of patients obtain a partial or complete response and therefore prove to be chemo-sensitive. An alternative regimen that seems to be effective in this setting is the VIM (etoposide, ifosfamide, methotrexate) regimen[8]. Herbrecht and colleagues[8] demonstrated a high response rate in patients with relapsing non-Hodgkin's lymphoma. However, no data are available regarding whether an alternating scheme of DHAP and VIM might be more effective as it makes use of more non-cross-resistant chemotherapeutic agents.

In the present prospective randomized trial we report the effects of granulocyte-macrophage (GM)-CSF-mobilized autologous peripheral blood stem cells compared with autologous bone marrow reinfused after high-dose myeloablative chemotherapy with regard to haematological reconstitution, supportive care, cost-effectiveness and quality of life in patients with progressive recurrent lymphoma treated according to the DHAP-VIM-DHAP regimen. The results indicate that PSCT is superior to ABMT with respect to those parameters.

Patients and methods

Study design

This was a multicentre, randomized phase III trial involving patients with relapsed/progressive lymphoma conducted between 1994 and 1998 in the Netherlands by the Hovon study group. The ethics committee at each institution approved the study and informed consent was obtained from all patients. After verification of inclusion and exclusion criteria patients were centrally randomized. The

randomization was stratified by centre, by Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL), and, by a ratio of 2:1, to receive peripheral blood stem cells or autologous bone marrow.

Patient selection and treatment

Two hundred and four patients with relapsed/progressive intermediate- or high-grade NHL (n= 166) or HD (n=38) were enrolled. Patients received induction chemotherapy consisting of DHAP-VIM-DHAP. The DHAP regimen consisted of cisplatin (100mg/m^2) on day 1 via continuous infusion over 24 hours, followed day 2 by cytarabine at 2 g/m^2 in a 3-hour infusion dose, repeated after 12 hours. Dexamethasone, 40 mg given orally or i.v., was also administered for four consecutive days. The VIM regimen consisted of etoposide (90 mg/m^2) i.v. on days 1, 3, and 5; ifosfamide (1200 mg/m^2 i.v.) on days 1-5; and methotrexate (30 mg/m^2 i.v.) on days 1 and 5. These chemotherapy regimens were given at 3- to 4-weekly intervals. After the VIM chemotherapy course, patients with a partial (> 50% reduction in tumour mass) or complete response and a negative bone marrow biopsy were randomized to receive bone marrow or peripheral blood stem cells.

Bone marrow or peripheral stem cell collection

Bone marrow stem cells were collected after the VIM chemotherapy in patients having stable peripheral blood counts. Autologous bone marrow was harvested from both posterior iliac crests under general anesthesia as per local practice. A minimum yield of 1 x 10^8 nucleated cells/kg body weight was required. Bone marrow purging was not performed. Patients randomized to undergo PSCT received 5 µg/kg GM-CSF (Molgramostim) daily by subcutaneous injection (kindly provided by Novartis Pharma Basel) starting 4 days after the second DHAP chemotherapy course until the final leukapheresis. The leukapheresis was undertaken at a leukocyte count of 1.0-2.0 x 10^9/l and a platelet count > 50 x 10^9/l. A minimum target collection of 20 x 10^4 granulocyte-macrophage colony-forming units (GM-CFU)/kg and 2 x 10^6 CD34$^+$ cells/kg was attempted in each patient. Marrow harvest and leukapheresis products were cryopreserved according to standard procedures at each centre. When an inadequate number of bone marrow stem cells or peripheral blood stem cells was collected, an additional bone marrow harvest or peripheral stem cell collection was allowed.

Bone marrow harvests and leukapheresis products were characterized by counting the numbers of nucleated cells and assaying the number of CFU-GM in semisolid culture systems. In addition, the number of CD34$^+$ cells were determined in the leukapheresis product using FACS analysis according to standard procedures[9].

Conditioning regimen and reinfusion of stem cells

All patients received high-dose chemotherapy according to the BEAM (carmustine, etoposide, cytarabine, melphalan) protocol. This included administration of carmustine (300 mg/m^2) on day -6, etoposide (200 mg/m^2) and cytarabine (200 mg/m^2) on days -5 to -2, and melphalan (140 mg/m^2) on

day -1. The cryopreserved bone marrow or peripheral blood stem cells were thawed and reinfused on day 0, at least 24 hours after completion of BEAM[10].

Supportive care and clinical monitoring

Antibiotic prophylaxis to decontaminate the gastrointestinal tract was applied at a neutrophil count < 0.5 x 10^9/l according to local protocols in the various centres. No haematopoietic growth factors were applied after the infusion of stem cells. Therapeutic antibiotic, antiviral, and antimycotic treatment was left to the discretion of the investigator, but it was initiated at least at a body temperature > 38.5°C after two readings taken 2 hours apart, and the treatment was to be discontinued once the patient had remained afebrile for 72 hours. Irradiated platelet transfusions were scheduled to be given if the platelet count was < 10 x 10^9/l or in cases of significant bleeding at higher counts. Irradiated red blood cells were transfused according the policy of each institution. Complete blood counts and vital signs were monitored daily during hospitalization. Afebrile patients not requiring intravenous treatment were discharged from the hospital at a neutrophil count of > 0.5 x 10^9/l measured on two different days.

Quality of life analysis

Quality of life was measured by written self-report questionnaires on three occasions: the day before transplantation, 14 days post-transplantation and 3 months after discharge from the hospital. Generic questionnaires used were the EuroQol and the SF-36[11] (the latter one was not used at the 14 days post-transplantation time point). The Rotterdam Symptom Checklist (RSCL) was used as a cancer-specific questionnaire. The EuroQol questionnaire consists of two parts. The first part is a generic five-dimensional questionnaire, the EQ-5D. This profile can be transformed to a value given by the general public: the $EQ\text{-}5D_{index}$[12]. The second part of the EuroQol questionnaire is a visual analogue scale, the EQ_{VAS}, which represents the patient's judgement of his own health state. The SF-36 measures functional status, well-being and general health perception on nine subscales, which can be aggregated into two sum scores, physical health and mental health[13]. The RSCL mainly measures disease-specific items, such as nausea and lack of energy. Items were added to measure complaints concerning painful joints, palpitations, rash, sweating and shivering.

Cost analysis

Total costs per patient were determined for the entire trial period, running from the start of the first DHAP chemotherapy course until 3 months after hospital discharge following the transplantation. Within this time interval, the total costs were based on the total numbers of all medical procedures, medications, diagnostic tests, laboratory services, hospital days, daycare treatments and outpatient visits per patient. For each patient, these numbers were obtained from hospital information systems and patient records in all six participating centers in the trial.

Actual costs of the most important items were calculated using financial data from the two hospitals with the highest number of patients in the trial (1997 level, 1 US$ = 2.37 Dutch Guilders). Costs were

split into direct costs (including personnel, materials, disposables, equipment, laundry and regular nutrition) and indirect costs (overhead). Costs of a haematology hospital day, including costs of a possible stay in a protected environment amounted to $303 (direct costs were $198). A haematology outpatient visit cost $71 (direct costs: $52) and a daycare treatment for chemotherapy administration or blood transfusion amounted to $137 (direct costs: $64). The procedure costs of stem cell harvesting (consisting of 2 leukapheresis) were $909. The costs of freezing and thawing were $781 and $168 respectively. Total procedure costs of the stem cell transplantation were therefore $1858. For bone marrow transplantation, total procedure costs were $2009 (of which $ 1243, $618 and $148 were for harvesting, freezing and thawing respectively). For items that had low costs or only a negligible influence (owing to low average numbers), Dutch 1997 tariffs were used as an approximation. Costs of medication were based on Dutch wholesale prices[14].

Study endpoints

The primary objective of this study was to determine the kinetics of engraftment of neutrophils ($\geq$ 0.1 and 0.5 x 10^9/l), platelets (> 20 x 10^9/l without transfusions) after PSCT or ABMT and the duration of hospitalization. Secondary endpoints included the number of platelet and red blood cell transfusions, the number of documented infections, the number of days with fever and antibiotic treatment, and the number of days with haemorrhage.

Statistical analysis

Analysis was performed for the intention-to-treat (ITT) as well as the per protocol (PP) population. The PP population consisted of those patients who were transplanted according to the treatment assigned at randomization.

In those situations where engraftment did not take place before discharge or if a missing value occurred, the date of engraftment was estimated using a linear interpolation method.

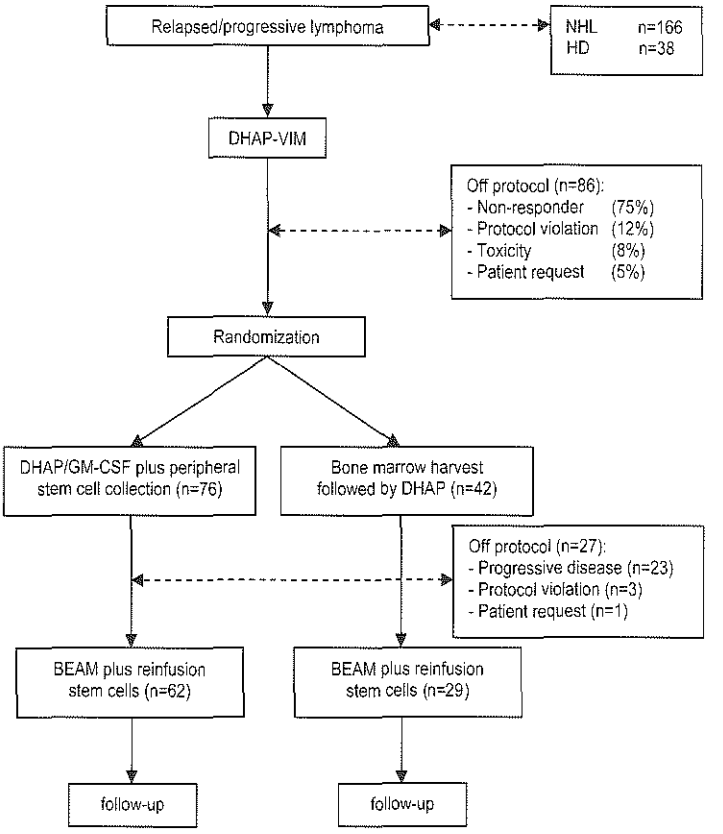
Baseline characteristics and the primary and secondary variables were compared between the two treatment groups using Student's t-test, Wilcoxon two-sample test, Fisher's exact test or a chi-squared test as appropriate. Clinical data are reported as median with range or as percentages. Costs and quality-of-life data are presented as mean values with ranges. Furthermore, Kaplan-Meier survival curves are presented for disease-free survival and overall survival. All statistical analyses were two-sided, using a 5% significance level. P values calculated for baseline characteristics and secondary variables should be interpreted descriptively. Analysis was performed using SAS version 6.12 (SAS Institute, Cary, NC, USA).

Results

Patients

From September 1994 until November 1998, 204 patients were enrolled in the study (Figure 1). These included 166 patients with of intermediate or high-grade NHL with first relapse after an adriamycin-containing regimen (n=151) or progressive during an adriamycin-containing regimen (n=15), and 38 patients with relapsed HD. All patients were treated using a DHAP and VIM chemotherapy course. After the two chemotherapy courses, 118 patients obtained a complete (15%) or partial response (43%) and were randomized (95 patients with NHL and 23 patients with HD). In total, 86 patients were not randomized owing to non-responsive/progressive disease (75%), toxicity (8%), patient request (5%) and protocol violation (12%).

Figure 1. Flow chart of patient numbers during different treatment stages.



Seventy-six patients were randomized to receive peripheral stem cells and 42 patients to receive autologous bone marrow. The disease characteristics of these patients are shown in Table 1. There were no significant differences between the two treatment groups in terms of age, sex, diagnosis, treatment history, disease status and the number of patients with a serum lactate dehydrogenase (LDH) level above two times the normal upper limit. Of the 118 patients randomized, 91 patients were transplanted. Twenty-seven patients were withdrawn from the study before BEAM high-dose therapy owing to progressive disease (n=23), patient request (n=1) or protocol violation (n=3). Finally, 29 patients received autologous bone marrow reinfusion and 62 patients received a peripheral stem cell infusion.

Table 1. Patient characteristics of the randomized patients.

	PSCT (n=76)	ABMT (n=42)
Median age, years (range)	51 (18-64)	50 (18-63)
Men/women (%)	63/37	54/45
Non-Hodgkin's lymphoma	62	33
Hodgkin's disease	14	9
Previous chemotherapy (%)	100	100
Previous radiotherapy (%)	29	31
Lactate dehydrogenase above 2x upper limit (%)	9	10
Stage of the disease:		
- I/II (%)	38	34
- III (%)	23	30
- IV (%)	38	32

PSCT, peripheral stem cell transplantation; ABMT, autologous bone marrow transplantation.

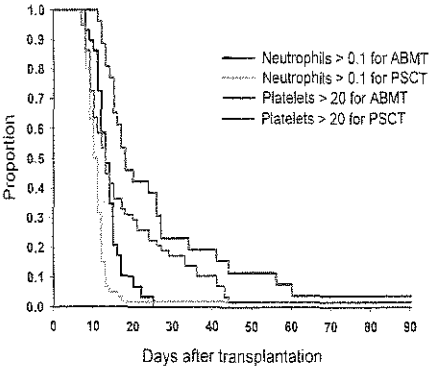
Quality of the bone marrow or peripheral blood stem cell graft

In 37 patients, autologous bone marrow stem cells were harvested. A median of 1.0 x 10^8 (0.1-37) nucleated cells/kg was collected and 7.6 (0.9-152) x 10^4 GM-CFU/kg. In two patients, an inadequate stem cell graft was obtained (0.0 and 1.0 x 10^8 nucleated cells/kg). In these patients an additional peripheral blood stem cell harvest was performed containing 0.18 and 3.8 x 10^6 $CD34^+$ cells/kg. In 74 patients, peripheral stem cells were harvested following the second DHAP chemotherapy course and GM-CSF. GM-CSF was applied for 12 days (9-21). A median of two leukapheresis (1-5) were required to collect a median of 4.4 x 10^6 $CD34^+$ cells/kg (0.2-25). In five patients, < 2 x 10^6 $CD34^+$ cells /kg were harvested. In these five patients and two other patients an additional bone marrow collection was performed. In these seven patients the graft contained a median of 5.40 x 10^4 CFU-GM/kg (0.3-41).

Haematopoietic recovery

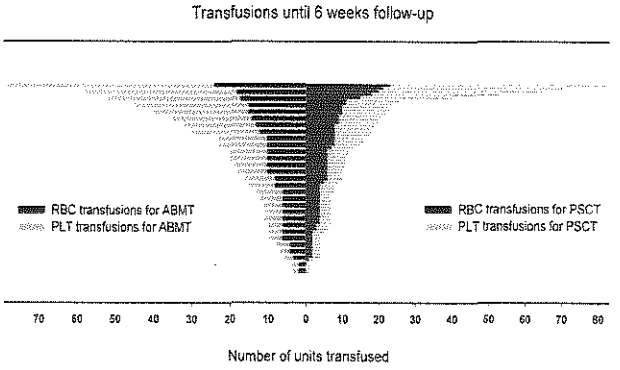
Following high-dose chemotherapy with BEAM, a significantly faster engraftment was observed after PSCT than after ABMT (Figure 2). In the PSCT group, a neutrophil count > 0.1 x 10^9/l and 0.5 x 10^9/l was observed after a median of 10.5 days (7-36) and 15 days (9-45), respectively, while in the ABMT group these values were 13 days (8-25) and 26 days (14-80) respectively (P< 0.01). A leukocyte count > 1.0 x 10^9/l was obtained after 14 days (9-42) in the PSCT arm and 21 days (11-40) in ABMT arm. A similar pattern was observed for platelet engraftment. In the PSCT group, an unsupported platelet count of > 20 x 10^9/l was reached after 13 days (7-51). These values were reached in the ABMT group after 18 days (11-65, P< 0.01). The patients in the PSCT arm also received fewer

Figure 2. Engraftment of granulocytes and thrombocytes after PSCT and ABMT. Non-engraftment was observed for neutrophils (n=2, PSCT); platelets (n=4; ABMT (n=2), PSCT (n=2)).



transfusions of platelets and red blood cells (Figure 3). A median of 4 units of platelet transfusions (0-60) were given to the PSCT group whereas the ABMT group received eight transfusions (2-55, P= 0.02). In total, a median of 6 units (0-23) of red blood cell transfusions were given in the PSCT arm and 8 units (2-24, P< 0.01) in the ABMT arm.

Figure 3. Number of red blood cell transfusions (RBC) and platelet transfusions until 6 weeks post transplantation.



Infectious complications and haemorrhage

Patients in the PSCT arm had fewer days with fever than patients in the ABMT group; a median of 4 days (0-15) versus 6 days (0-25) respectively (P= 0.07). A similar pattern was observed with regard to the number of days with intravenous antibiotics in patients with fever [8.5 (0-30) versus 14 days (0-34), P= 0.04]. Documented infections were observed in 51% of the PSCT patients and in 45% of the ABMT patients and consisted primarily of bacteraemia with gram-positive bacteria (Table 2). No significant difference in the number of haemorrhagic events was observed between both groups (P= 0.31).

Table 2. Frequency of suspected and documented infections during different forms of stem cell transplantation.

	PSCT	ABMT
Suspected infections (%)	39	38
Documented infections (%)	51	45
- Bacteraemia*		
gram-positive bacteraemia	11	5
- Central line		
gram-positive bacteraemia	9	2
gram-negative bacteraemia	0	1
- Mucositis as a result of herpes simplex	8	7
- Sputum aspergillus	0	1

* Number of events.

Quality-of-life analysis

The main scores on the quality-of-life measurements are reported in Table 3. Regarding the EuroQol and the SF-36, there were no significant differences between both trial arms. On the RSCL, several items differed significantly between both arms (P< 0.05). Fourteen days after the transplantation, ABMT patients reported more complaints concerning tiredness, lack of energy, headache and dizziness. Of the added items to the RSCL, palpitations, rash, sweating and shivering were reported

significantly more often in the ABMT arm. Three months after discharge from the hospital, ABMT patients reported more complaints about nausea, vomiting and shivering.

Scores on the individual items of the RSCL can be summarized into three domain scores: physical complaints, mental complaints and an activity score. On day 14 after transplantation, the physical complaints domain score was significantly higher in the ABMT arm. The activity score of the PSCT arm was significantly better on both day 14 after transplantation as well as 3 months after discharge.

Table 3. Quality-of-life measurements.

Trial arm	Measurement	Day before transplantation	14 days after transplantation	3 months after hospital discharge
PSCT	EQ_{VAS}	68	55	73
	$EQ\text{-}5D_{index}$	75	53	78
	SF-36 PCS	40.1	-	40.8
	SF-36 MCS	48.1	-	52.9
	RSCL PSDL	20.1	34.5	15.7
	RSCL PDL	19.4	22.3	17.5
	RSCL ALI	63.2	48.4	68.9
	RSCL-i (1^{st})	Loss of hair (2.43)	Lack of appetite (3.02)	Tiredness (2.59)
	RSCL-i (2^{nd})	Tiredness (2.21)	Loss of hair (2.90)	Sore muscles (1.90)
	RSCL-i (3^{rd})	Difficulty concentrating (2.14)	Sore mouth, pain when swallowing (2.75)	Worrying (1.85)
	RSCL-i (4^{th})	Lack of energy (1.88)	Nausea (2.58)	Dry mouth (1.85)
	RSCL-i (5^{th})	Worrying (1.85)	Tiredness (2.55)	Lack of energy (1.83)
	RSCL-i (6^{th})	Difficulty sleeping (1.79)	Dry mouth (2.53)	Shortness of breath (1.71)
ABMT	EQ_{VAS}	66	50	70
	$EQ\text{-}5D_{index}$	78	42	77
	SF-36 PCS	39.2	-	38.1
	SF-36 MCS	47.1	-	52.0
	RSCL PSDL	22.9	43.9	21.2
	RSCL PDL	24.0	20.8	23.0
	RSCL ALI	59.8	32.1	62.9
	RSCL-i (1^{st})	Loss of hair (2.78)	Loss of hair (3.50)	Tiredness (2.57)
	RSCL-i (2^{nd})	Tiredness (2.29)	Lack of appetite (3.41)	Dry mouth (2.22)
	RSCL-i (3^{rd})	Difficulty concentrating (2.21)	Sore mouth, pain when swallowing (3.32)	Sore muscles (2.13)
	RSCL-i (4^{th})	Lack of appetite (2.00)	Tiredness (3.27)	Lack of energy (2.13)
	RSCL-i (5^{th})	Worrying (2.00)	Lack of energy (3.09)	Worrying (2.04)
	RSCL-i (6^{th})	Nausea (1.92)	Dry mouth (2.95)	Difficulty concentrating (1.96)

Scores in both trial arms on EuroQol Visual Analogue Scale (EQ_{VAS}), EuroQol 5 Dimension Index ($EQ\text{-}5D_{index}$), SF-36 Physical Composite Score (SF-36 PCS), SF-36 Mental Composite Score (SF-36 MCS), Rotterdam Symptom Checklist Physical Symptom Distress Level (RSCL PSDL), RSCL Psychological Distress Level (RSCL PDL), RSCL Activity Level Impairment (RSCL ALI) and the six highest RSCL items scores (RSCL-i). Ranges (worse to best) are 0-100 (EuroQol, SF-36, RSCL ALI), 100-0 (RSCL PSDL, RSCL PDL) and 4-1 (RSCL-i).

Cost analysis

Costs of the DHAP-VIM-DHAP induction chemotherapy preceding the transplantation amounted to $10395 for the entire trial group. On average, patients were hospitalized 4.05 days for stem cell harvesting and 4.08 days for bone marrow harvesting. Total costs of the harvesting phase were $4631 in the PSCT arm and $4409 in the ABMT arm (P= ns).

The costs after the harvesting phase until the transplantation phase amounted to $446 in the PSCT arm and $1484 in the ABMT arm (P= ns).

In the transplantation phase (starting with BEAM chemotherapy), patients were hospitalized for a mean duration of 27 days in the PSCT arm (range: 8-51) and 34 days in the ABMT arm (range 24-78; P< 0.05), which amounted to hospitalization costs of $8435 (range $3034 - $19000) and $10444 (range $7281 - $25427) respectively. Costs of antibiotics were significantly lower in the PSCT arm than in the ABMT arm ($837 and $1465 respectively; ranges $1 - $2964 and $20 - $4797). As the costs of hospitalization were the main drivers of the total costs, the total costs in the transplantation phase were significantly lower in the PSCT arm ($13954; range: $4913 - $29532) than in the ABMT arm ($17668; range $10170 - $44082). The costs of 3 months of follow-up after discharge did not differ between both arms (PSCT: $1943, range $88 - $10912; ABMT: $2872, range $287 - $14130).

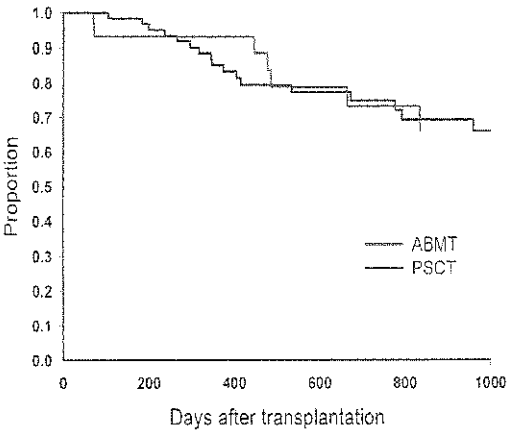
Survival

Transplantation-related mortality < 100 days was not different in either group. In the PSCT arm, two patients died as a result of progressive disease, and, in the ABMT arm, one patient died as a result of cytomegalovirus pneumonitis.

The disease-free survival rate from randomization was 39% in the PSCT arm and 45% in the ABMT arm after a median follow-up of 460 days (P= ns; Figure 4). No difference was noted between patients with NHL versus HD, 41% versus 43% respectively.

Discussion

Figure 4. Survival of patients in the different transplantation arms. ABMT, autologous bone marrow transplantation; PSCT, peripheral stem cell transplantation.



The present study demonstrates that autologous peripheral blood stem cell transplantation is cost-effective and superior with regard to engraftment kinetics, supportive care and discharge from hospital than ABMT. To date, a limited number of studies have addressed these questions and have compared their data with a historical control group[1, 2]. The study of Schmitz and colleagues[4] demonstrated an advantage of PSCT over ABMT. The median time to unsupported platelet recovery is similar in both studies. However, with regard to granulocyte recovery, a distinctly faster recovery was noted by Schmitz and colleagues[4], which might in part be owing to the application of G-CSF post-transplantation. The benefit of in vivo G-CSF application seems to apply to the ABMT arm in particular. However, there is a great variability in neutrophil recovery in the setting of ABMT, which will

be related to previous chemotherapy regimens and the number of (stem) cells collected. Damiani and colleagues[15] reported a median of 13 days for neutrophil engraftment in ABMT patients. In contrast, a recent study with recombinant interleukin 3 (IL-3) given in the setting of ABMT demonstrated a neutrophil ($\geq$ 0.5 x 10^9/l) and platelet ($\geq$ 20 x 10^9/l) engraftment in the placebo arm after a median of 25 and 28 days respectively[16]. These findings are in line with the results obtained in the present study. The advantage in the granulocyte and platelet recovery in the PSCT arm was also reflected in a significant reduction in number of days with fever and intravenous antibiotics, and less transfusions, further underscoring the advantage of applying PSCT over ABMT. A recent study suggested that the results of ABMT could be improved by using G-CSF-exposed bone marrow cells for 3 days[15]. In this setting, the difference in engraftment between PSCT versus ABMT almost disappeared. This may be related to the fact that the collected bone marrow cells contain a mixture of bone marrow and peripheral blood stem cells.

The results of the cost analysis and the quality-of-life study demonstrated that no differences in costs were observed for the procedure of stem cell collection. Comparison with other studies can hardly be made owing to different methodologies, assumptions and large variations in unit costs between countries. However, the published studies to date are in line with our results[17, 18]. The main difference between both arms was observed during the transplantation phase. The lower costs of the PSCT arm were as a result of the shorter period of hospitalization and the lower costs of antibiotics, which are linked to a faster recovery of the granulocyte count. The better quality-of-life scores might also be related to this finding.

The results obtained with the DHAP-VIM regimen do not seem to differ from studies using either DHAP or VIM, although in the present study more non-cross-resistant chemotherapeutic agents were used[6, 8]. The major reason for discontinuation of chemotherapy in the present study was progressive/non-responsive disease in 40-50% of the patients before high-dose chemotherapy could be given. Alternative regimens do not seem to improve the results. A number of patients with progressive disease after DHAP-VIM were treated with a mini-BEAM regimen[19]. All the non-Hodgkin's lymphoma patients were non-responsive, while some patients with HD were responsive and obtained long-term survival after transplantation. These results indicate that new approaches are warranted to improve the results in this patient group. Future studies with monoclonal antibodies, radiolabelled CD20, or immunotherapy in combination with chemotherapy, will reveal whether these alternatives are more effective and will enlarge the group of chemo-sensitive patients before PSCT.

In summary, the results of the present prospective randomized study demonstrated that PSCT was superior to ABMT in patients with chemosensitive lymphoma, not only with regard to engraftment but also to cost-effectiveness and quality of life.

Acknowledgements

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Chapter 5. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease: a prospective randomised trial

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Abstract

The cost-effectiveness of autologous peripheral blood stem cell transplantation (PBSCT) compared with autologous bone marrow transplantation (ABMT) for refractory or relapsed non-Hodgkin's lymphoma (NHL) or Morbus Hodgkin (MH) was assessed.

Costs were determined from the induction chemotherapy regimen up to 3 months after discharge from hospital following the transplantation. Quality of life was measured by the EuroQol, the Rotterdam Symptom Checklist (RSCL) and the SF-36. Patients were randomised according to a 2:1 ratio to undergo either PBSCT or ABMT. 62 patients underwent PBSCT and 29 ABMT. Costs of the transplantation period were significantly lower in the PBSCT group (€15008) than in the ABMT group (€19000). Significant differences in quality of life were all in favour of PBSCT and emerged using the RSCL, both on 14 days after the transplantation and three months after discharge. We conclude that PBSCT is associated with lower costs and a better quality of life than ABMT for patients with refractory or relapsed NHL or MH.

Introduction

For patients with refractory or relapsed Morbus Hodgkin (MH) or non-Hodgkin's lymphoma (NHL) of intermediate or high-grade malignancy, intensive chemotherapy followed by autologous bone marrow transplantation (ABMT) has been the preferred treatment since Philip and colleagues demonstrated its superiority over single intensive chemotherapy in patients with NHL[1, 2]. A few years ago, haematopoietic growth factors (HGF) became available, allowing the collection of haematopoietic stem cells from the peripheral blood after chemotherapy and HGF administration. In their prospective randomised trial, Klumpp and colleagues found that HGF adminstration in patients undergoing PBSCT with or without autologous bone marrow accelerated the rate of neutrophil engraftment, shortened the duration of hospitalisation, and reduced the number of days on nonprophylactic antibiotics[3]. Due to these advantages, HGF mobilised PBSCT has now largely replaced ABMT[4, 5]. In a prospective randomised trial, PBSCT was found to be superior to ABMT in patients with NHL or MH with regard to platelet recovery[6]. Patients randomised to PBSCT needed fewer red blood cell transfusions and spent less time in the hospital. As hospital days are often one of the main components of the total costs in economic evaluations and PBSCT avoids anaesthesia and operating room procedures, an economic advantage of PBSCT over ABMT may be expected. Such an advantage was indicated retrospectively in cost analyses by several authors[7-11] and confirmed prospectively by Hartmann and colleagues[12]. Only a relative small number of studies have so far addressed the cost-effectiveness of PBSCT[13], although it is a topic of considerable interest. As the increase in the incidence of NHL is sustained, stem cell transplantations continue to be a significant burden on healthcare resources[14]. To our knowledge, it has not yet been studied to what extent the quality of life of these patients shortly after transplantation is affected and, particularly, if any differences in quality of life of patients having undergone either PBSCT or ABMT can be observed. Therefore, we performed a comprehensive cost-effectiveness analysis, including quality of life measurements, using data from a prospective multi-centre trial in which patients with refractory or relapsed NHL or MH were randomised to receive either ABMT or HGF mobilised autologous PBSCT after having undergone a three-cycle induction chemotherapy regimen followed by high-dose conditioning chemotherapy. The clinical findings of this study have been reported separately[15]. In this article, the results of the cost-effectiveness analysis are reported in detail.

Patients and methods

Study population

The study population comprised patients aged 18-65 years with intermediate or high-grade MH or NHL who relapsed after or were refractory to primary chemotherapy. This randomised phase III trial

was performed in six centres in the Netherlands between 1994 and 1998 (five university hospitals and one cancer centre).

Study design

All patients underwent induction chemotherapy, consisting of a DHAP course and a VIM course, separated by a 3-4 week interval. DHAP consisted of cisplatin (100 mg/m^2) on day 1 by a 24-hours continuous infusion, cytarabine (2 g/m^2) on day 2 by a 3-hours infusion which was repeated after 12 hours, and dexamethasone (40 mg orally or intravenously (i.v.)) administered daily on days 1-4. VIM consisted of etoposide (90 mg/m^2) i.v. on days 1, 3, and 5, ifosfamide (1200 mg/m^2) i.v. on days 1-5 and methotrexate (30 mg/m^2) i.v. on days 1 and 5. Patients who showed a partial (>50% tumour mass reduction) or complete response and a negative bone marrow biopsy after VIM were randomised according to a 2:1 ratio to undergo either PBSCT or ABMT. The remainder of the treatment consisted of another DHAP course and a high-dose conditioning chemotherapy regimen consisting of carmustine (300 mg/m^2) on day -6 (from graft reinfusion), etoposide (200 mg/m^2) and cytarabine (200 mg/m^2) on days -5 to -2, and melphalan (140 mg/m^2) on day -1 (the BEAM regimen). The graft was reinfused on day 0. In the PBSCT group, the harvesting of the stem cells had taken place by leukapheresis after the second DHAP course followed by granulocyte macrophage-colony stimulating factor (GM-CSF) treatment 5µg/kg daily from the fourth day after the second DHAP course until the last leukapheresis (Leucomax®, Novartis, Basle, Switzerland). In the ABMT group, the bone marrow was harvested from the pelvis under general anaesthesia, prior to the second DHAP course (see reference 15 for an extensive description of the design).

Costs

In this analysis, the institutional perspective was taken[16]. The average total costs per patient were determined for the entire trial period, running from the start of the first DHAP course up to 3 months after hospital discharge after transplantation. The cost analysis was based on a database with all medical procedures, diagnostic tests, laboratory services, hospital days, daycare treatments and outpatient visits of all trial patients that were transplanted.

In contrast to charges, unit costs are the best estimators of the theoretically proper opportunity costs[16]. Therefore, we determined average unit costs for the most important cost items of our analysis (Table 1), reflecting real resource use, including a raise for overhead costs[17]. To determine the use of resources, we mainly followed the micro-costing method, which is based on a detailed inventory and measurement of all resources consumed[18]. The valuation of the resources and overhead costs was based on data from the financial departments of the two (university) hospitals with the highest number of patients in the trial (1997 level, 1 Euro = 2.20371 Dutch Guilders). In each unit cost, a distinction to personnel costs (P), material costs (M) and overhead costs (O) was made. P included wages, social premiums, and fees for irregular working hours of the haematologist, registrars, nursing staff and administrators. The haematologists and registrars were asked to estimate the time spent for each

individual patient during a hospital day and an outpatient visit. Costs of nursing staff and administrators were calculated by dividing their total annual costs in the haematology department by the total annual number of hospital days. M comprised costs of disposables, equipment, regular nutrition (parenteral nutrition was calculated separately), laundry services and cleaning services. O contained bare hotel costs (without the already mentioned laundry and cleaning costs) and the costs of non-medical departments of the hospital, like general management. The latter costs were not specifically known for the haematology department. Therefore, the total annual hospital costs on this item were determined, after which a part of these costs were allocated to the haematology department on the basis of the percentage square meters of the haematology department compared with the total amount of square meters of the entire hospital.

The unit costs are shown in Table 1. The unit cost of a haematology inpatient hospital day included costs for a possible stay in one of the isolation rooms of the haematology department. It also included costs of one 10-minutes visit (and 10 minutes of related work) of the haematologist during each hospital day. The latter is also included in the costs of an intensive care hospital day. An outpatient visit was assumed to take 15 minutes of the haematologist's time and an additional 15 minutes on work resulting from this visit. Costs of an outpatient stay on the daycare ward were particularly based on the resource use necessary for the administration of blood components. The costs of stem cell harvesting were based on an average number of two leukaphereses. The harvesting costs contain costs of 5.5 hours of a research nurse's time and 1 hour of the haematologist's time per leukapheresis. Material costs for bone marrow harvesting were higher than for stem cell harvesting as the former procedure was performed in the operating room. These fixed costs for stem cell transplantations and bone marrow transplantations were assumed to be the same for all patients who underwent PBSCT or ABMT, respectively.

For items with low costs or a neglectable influence (due to low average numbers), Dutch 1997 tariffs (of the Central Organ for Tariffs in Health Care, COTG) were used as approximations. Costs of medication were based on Dutch wholesale prices[19].

Table 1. Unit costs (in Euros).

	Personnel	Materials	Overhead	Total
Haematology inpatient hospital day	160	53	113	326
Intensive Care Unit hospital day	530	166	252	948
Outpatient visit	52	4	20	76
Outpatient stay on daycare ward	29	40	79	148
Radiotherapy megavolt session	99	16	48	163
PBSCT				
- Harvesting	366	417	196	979
- Freezing	225	447	168	840
- Defrosting	127	18	36	181
ABMT				
- Harvesting	442	627	267	1336
- Freezing	254	278	133	665
- Defrosting	110	17	32	159

PBSCT, peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation

Quality of life

Economic evaluations require the use of a generic (non-disease-specific) instrument for health status measurement[20]. Therefore we used the EuroQol and the SF-36. In addition, the Rotterdam Symptom Checklist (RSCL) was applied as a cancer-specific questionnaire that is more sensitive to changes in health states of cancer patients. These instruments were included in written self-report questionnaires that were administered three times: the day before transplantation, 14 days post transplantation and 3 months after discharge from the hospital. The SF-36 was not included in the second measurement, since the majority of questions in this questionnaire are not applicable to hospitalised patients.

The EuroQol questionnaire exists of two parts. The first part is a generic five-dimensional questionnaire, the EQ-5D. This profile can be transformed to a value given by the general public: the $EQ\text{-}5D_{index}$[21]. The second part of the EuroQol questionnaire is a visual analogue scale, the EQ_{VAS}, which represents the patient's judgement of his own health state. The SF-36 measures functional status, well-being and general health perception on nine subscales which can be aggregated into two sum scores, physical health and mental health[22]. The RSCL mainly measures (cancer-specific) complaints by 38 items, such as nausea and lack of energy[23]. Five items were added to measure complaints that were related to possible adverse effects of the treatment under study: painful joints, palpitations, rash, sweating and shivering.

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows, release 9.0.0. The Mann-Whitney test was used for the between-group comparisons of quality of life and cost items, using a 2-sided probability level of ≤ 0.05. All data are presented as mean values.

Table 2. Characteristics of the transplanted patients and main clinical findings[15].

	PBSCT (n=62)	ABMT (n=29)	P value
Mean age (median, range) (years)	49 (51; 18-64)	46 (50; 18-63)	0.32
Male / female (%)	68/32	48/52	0.11
NHL / MH (%)	85/15	72/28	0.16
Previous chemotherapy (%)	100	100	1.00
Previous radiotherapy (%)	32	35	1.00
LDH above 2x upper limit (%)	10	7	1.00
Time to neutrophil recovery (median days)	10	15	<0.01
Time to platelet recovery (median days)	13	18	<0.01
Red blood cell transfusions (median/patient)	6	10	0.02
Platelet transfusions (median/patient)	4	8	<0.02

NHL, Non-Hodgkin's lymphoma; MH, Morbus Hodgkin; LDH, lactate dehydrogenase.

Results

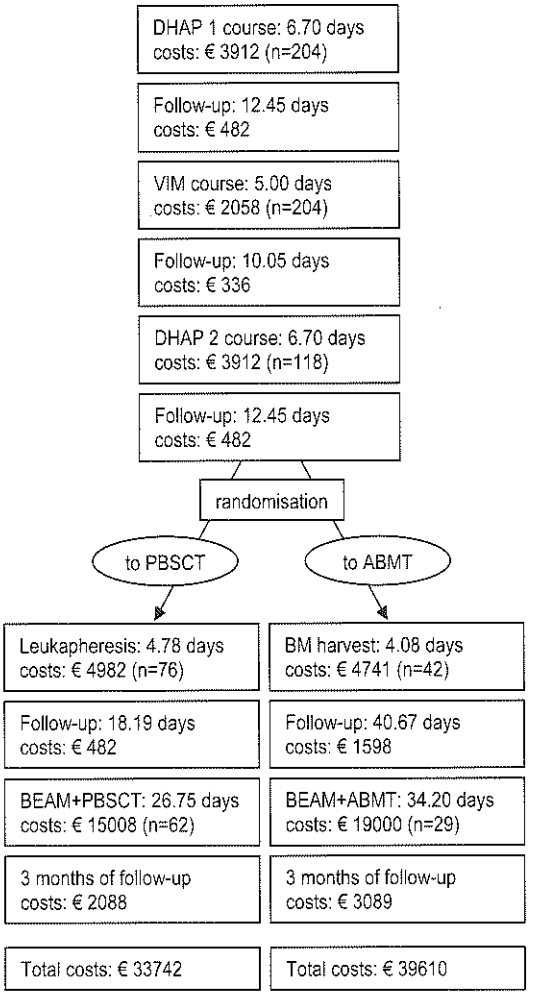
Patients

Characteristics of the 91 transplanted patients (62 PBSCT and 29 ABMT) and a summary of the clinical findings[15] are reported in Table 2.

Costs

The average total costs per patient of each distinct trial phase are presented in Figure 1. Costs of the DHAP-VIM-DHAP induction chemotherapy preceding the transplantation were € 11182 per patient on average (Table 3). Data on DHAP 1 costs were rarely available, as this course was primarily administered in referring hospitals. Costs of DHAP 1 + follow-up were therefore assumed to be equal to the costs of DHAP 2 + follow-up. Costs of the DHAP-VIM-DHAP regimen (including follow-up) were mainly determined by the costs of hospitalisation, as all courses were administered on an inpatient basis.

Figure 1. Average costs per patient of the entire trial treatment, average number of days per phase; BM, bone marrow; ABMT, autologous bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation.



Costs of the harvesting phase (Table 3) were € 4982 in the PBSCT arm and € 4741 in the ABMT arm (non-significant (n.s.)). Patients undergoing PBSCT, as well as patients undergoing ABMT, were hospitalised for 4 days on average during this phase. In the PBSCT arm, two leukaphereses were necessary on average to obtain a useful graft. As the stem cells were mobilised by HGFs in the PBSCT arm, the related costs were significantly higher for these patients. They were nevertheless outweighed by the higher procedural costs in the ABMT arm, caused by the costs of anaesthesia and use of the operating room. Costs of blood components were also significantly higher in the ABMT arm.

The total costs of the follow-up after the harvesting phase (Table 3) did not differ significantly between both trial arms (PBSCT: € 482; ABMT: € 1598), although in the ABMT arm costs of hospital days, haematology outpatient visits, antibiotics and blood components were significantly higher.

Table 3. Average total costs per patient (in Euros) during the induction chemotherapy regimen, during the harvesting phase and during the follow-up after the harvesting phase.

	DVD-ic	Harvesting phase			Follow-up after harvesting		
		PBSCT	ABMT	P value	PBSCT	ABMT	P value
Hospitalisation	6161	1468	1332	0.662	-	392	0.025
Daycare ward stay	134	25	-	0.307	8	98	0.026
Haematology outpatient visits	253	-	-	-	79	259	0.027
Consultations	35	4	25	0.026	122	55	0.125
Harvesting of transplant	-	979	1336	-[a]	-	-	-
Freezing of transplant	-	840	665	-[a]	-	-	-
Radiation therapy	158	-	-	-	-	-	-
Total parenteral nutrition	23	-	-	-	-	-	-
Blood components	904	376	663	0.003	1	312	0.007
Cytostatics	1413	-	-	1.000	-	6	0.116
HGF	289	830	-	0.002	-	68	0.116
Antibiotics	197	121	15	0.614	-	29	0.025
Other medication	337	41	232	0.189	-	14	0.025
Pathology diagnostics	28	-	48	0.000	3	-	0.524
Laboratory diagnostics	758	114	155	0.877	147	130	0.871
Microbiological diagnostics	21	21	9	0.657	2	7	0.138
Radiodiagnostics	400	39	74	0.190	58	96	0.120
Nuclear diagnostics	-	-	-	-	-	40	0.116
Other diagnostics	32	12	7	0.171	6	3	0.249
Other procedures	39	112	180	0.548	56	89	0.541
Total costs per patient	11182	4982	4741	0.075	482	1598	0.271

DVD-ic, DHAP-VIM-DHAP induction chemotherapy regimen; HGF, haematopoietic growth factors; PBSCT, peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation.
[a] Not compared, as these costs were assumed to be the same for each patient.

The transplantation phase (Table 4) started with the high-dose conditioning BEAM chemotherapy regimen. In this phase, the PBSCT patients were hospitalised for a shorter time (26.75 days; range 8-51 versus ABMT 34.20; range 24-78 days), which caused significantly lower hospitalisation costs during this phase (€ 9072 per patient; range € 3263 - € 20434) compared with the ABMT arm (€ 11232; range € 7830 - € 27346). Costs of antibiotics were also significantly lower in the PBSCT arm. Since hospital days were the main components of the total costs in the transplantation phase, the average total costs per patient were also significantly lower in the PBSCT arm (€ 15008; range € 5284 - € 31761 versus € 19000; range € 10937 - € 47408).

The average costs per patient of the 3-month follow-up period (Table 4) did not differ significantly between both study arms (PBSCT: € 2088; range € 95 - € 11735; ABMT: € 3089; range € 309 - € 15196). The main costs during this phase were costs of the blood components and hospital days.

Table 4. Average total costs per patient (in Euros) during the transplantation phase (from high-dose conditioning BEAM chemotherapy regimen up to discharge from the hospital) and during the 3-month follow-up after the transplantation phase.

	Transplantation phase			Follow-up after transplantation		
	PBSCT	ABMT	P value	PBSCT	ABMT	P value
Hospitalisation	9072	11232	0.000	316	833	0.460
Daycare ward stay	-	-	-	221	290	0.372
Haematology outpatient visits	-	-	-	393	460	0.130
Consultations	108	124	0.714	52	39	0.867
Defrosting of transplant	181	159	-[a]	-	-	-
Radiation therapy	-	-	-	109	125	0.342
Total parenteral nutrition	243	321	0.222	3	1	0.755
Blood components	1680	2303	0.250	491	751	0.246
Cytostatics	809	710	0.012	-	-	-
HGF	13	53	0.059	-	-	-
Antibiotics	900	1575	0.038	8	1	0.750
Other medication	649	782	0.625	1	4	0.330
Pathology diagnostics	12	18	0.375	5	5	0.440
Laboratory diagnostics	752	904	0.039	197	282	0.187
Microbiological diagnostics	304	494	0.017	8	17	0.075
Radiodiagnostics	215	232	0.808	213	210	0.959
Nuclear diagnostics	16	5	0.779	46	49	0.919
Other diagnostics	30	81	0.052	8	2	0.235
Other procedures	24	7	0.335	17	20	0.701
Total costs per patient	15008	19000	0.0001	2088	3089	0.247

HGF, Haematopoietic growth factors; PBSCT, peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation; BEAM, see text (Patients and methods).
[a] Not compared, as these costs were assumed to be the same for each patient.

Quality of life

The main scores on the quality of life measurements are reported in Table 5. Regarding the generic EuroQol and the SF-36 measurements, there were no significant differences between both arms. On the RSCL, several items differed significantly. Fourteen days after the transplantation, ABMT patients reported more complaints concerning tiredness (P= 0.001), lack of energy (P= 0.004), headache (P= 0.025), dizziness (P= 0.041) and loss of hair (P= 0.012). Of the items that were added to the RSCL to measure possible adverse effects of the treatment under study, palpitations (P= 0.049), rash (P= 0.007), sweating (P= 0.020) and shivering (P= 0.002) were reported more often in the ABMT arm.

Three months after discharge from the hospital, ABMT patients reported more complaints about nausea (P= 0.023), vomiting (P= 0.012) and shivering (P= 0.011).

Scores on the individual items of the RSCL can be summarised into three domain scores: physical complaints, mental complaints and an activity score. On the 14th day after transplantation, the physical complaints domain score was significantly worse in the ABMT arm (43.9 versus PBSCT 34.5; P= 0.006). The activity score, referring to the patient's functional status, was significantly bettter in the PBSCT arm on both the 14th day after transplantation measurement (48.4 versus ABMT 32.1; P= 0.013) as well as the 3 months after discharge measurement (68.9 versus ABMT 62.9; P= 0.017).

Table 5. Mean scores in both trial arms on EuroQol Visual Analogue Scale (EQVAS), EuroQol 5 Dimension Index (EQ-5Dindex), SF-36 Physical Composite Score (SF-36 PCS), SF-36 Mental Composite Score (SF-36 MCS), SF-36 Physical functioning (SF-36 PF), SF-36 Role functioning-physical (SF-36 RP), SF-36 Bodily pain (SF-36 BP), SF-36 General health (SF-36 GH), SF-36 Vitality (SF-36 VT), SF-36 Social functioning (SF-36 SF), SF-36 Role functioning-emotional (SF-36 RE), SF-36 Mental health (SF-36 MH), Rotterdam Symptom Checklist (RSCL) Physical Symptom Distress Level (RSCL PSDL), RSCL Psychological Distress Level (RSCL PDL), RSCL Activity Level Impairment (RSCL ALI) and the six highest RSCL items scores (RSCL-i)[a].

	Day before transplantation		14 days after transplantation		3 months after hospital discharge	
Measurement	PBSCT	ABMT	PBSCT	ABMT	PBSCT	ABMT
EQ_{VAS}	68	66	55	50	73	70
$EQ\text{-}5D_{index}$	75	78	53	42	78	77
SF-36 PCS	40.1	39.2	-	-	40.8	38.1
SF-36 MCS	48.1	47.1	-	-	52.9	52.0
SF-36 PF	62.9	61.1	-	-	70.0	61.7
SF-36 RP	23.2	16.3	-	-	29.0	28.4
SF-36 BP	81.7	86.8	-	-	84.0	74.4
SF-36 GH	54.4	52.1	-	-	56.9	50.3
SF-36 VT	59.8	60.2	-	-	57.8	53.3
SF-36 SF	61.0	62.5	-	-	76.2	69.0
SF-36 RE	66.7	57.9	-	-	82.0	82.5
SF-36 MH	70.5	71.7	-	-	76.2	76.3
RSCL PSDL	20.1	22.9	34.5	43.9	15.7	21.2
RSCL PDL	19.4	24.0	22.3	20.8	17.5	23.0
RSCL ALI	63.2	59.8	48.4	32.1	68.9	62.9
RSCL-i (1st)	Loss of hair (2.43)	Loss of hair (2.78)	Lack of appetite (3.02)	Loss of hair (3.50)	Tiredness (2.59)	Tiredness (2.57)
RSCL-i (2nd)	Tiredness (2.21)	Tiredness (2.29)	Loss of hair (2.90)	Lack of appetite (3.41)	Sore muscles (1.90)	Dry mouth (2.22)
RSCL-i (3rd)	Difficulty concentrating (2.14)	Difficulty concentrating (2.21)	Sore mouth, pain when swallowing (2.75)	Sore mouth, pain when swallowing (3.32)	Worrying (1.85)	Sore muscles (2.13)
RSCL-i (4th)	Lack of energy (1.88)	Lack of appetite (2.00)	Nausea (2.58)	Tiredness (3.27)	Dry mouth (1.85)	Lack of energy (2.13)
RSCL-i (5th)	Worrying (1.85)	Worrying (2.00)	Tiredness (2.55)	Lack of energy (3.09)	Lack of energy (1.83)	Worrying (2.04)
RSCL-i (6th)	Difficulty sleeping (1.79)	Nausea (1.92)	Dry mouth (2.53)	Dry mouth (2.95)	Shortness of breath (1.71)	Difficulty concentrating (1.96)

PBSCT, peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation.
[a] Ranges (worse to best) are 0-100 (EuroQol, SF-36, RSCL ALI), 100-0 (RSCL PSDL, RSCL PDL) and 4-1 (RSCL-i).

Discussion

In a prospective randomised multi-centre trial, we analysed the costs and effects of patients with refractory or relapsed non-Hodgkin's lymphoma (NHL) or Morbus Hodgkin (MH) undergoing either autologous PBSCT or ABMT. Clinical results mainly comprised shorter times to neutrophil and platelet recovery, less red blood cell and platelet transfusions in the PBSCT patients[15]. These results confirm those found earlier in a prospective randomised trial in patients of NHL or MH patients[6]. In the transplantation phase of our analysis, costs in the PBSCT arm were significantly lower compared with the ABMT arm. This was particularly caused by an earlier discharge of PBSCT patients (26.75 versus 34.20 days from start of the conditioning chemotherapy). In addition, costs of antibiotics were significantly lower in the PBSCT arm. The cost advantage of PBSCT has only been observed before prospectively by Hartmann and colleagues[12] in patients with solid tumours and lymphomas and confirmed by Smith and colleagues[9] who based their conclusions on the prospectively gathered data by Schmitz and colleagues[6]. Regarding quality of life, we found no significant post-transplantation differences using the generic EuroQol and the SF-36 questionnaires, implying that the overall health state of the patients is comparable among the PBSCT and ABMT groups. However, on the cancer-specific Rotterdam Symptom Checklist (RSCL), several differences were found in favour of PBSCT, indicating that NHL/MH patients undergoing PBSCT suffer less from those unpleasant cancer- and treatment-related symptoms than their counterparts undergoing ABMT.

An advantage of our study is its multi-centre design. As stated by Waters and colleagues[13], important cost differences between hospitals can occur in clinical practice, which are less likely to be expressed in the results, if the average total costs in a trial are based on data from several centres. Furthermore, our cost analysis is based on actual unit costs, which are generally considered to be the best estimators of opportunity costs[16]. However, only direct medical costs were assessed. Indirect costs (costs of lost production due to absence from work) were not calculated. In our opinion, the inclusion of these costs would not have undermined our main findings as no differences in quality of life between both study arms were found on the generic EuroQol and SF-36 questionnaires, which are indicative for the general health state of patients and the ability to work.

Our follow-up period was relatively short. Nevertheless, it contains an assessment of three months follow-up after discharge which has never been made before in prospective trials regarding costs of PBSCT versus ABMT treatment[14]. An indication for a slight (non-significant) cost advantage of PBSCT follow-up over the ABMT follow-up was found during these 3 months. The assessment of a longer follow-up period is unlikely to alter our main findings, since there is no evidence to indicate that follow-up costs after discharge would reverse the results[12]. The similar post-transplant morbidity, mortality and overall survival between PBSCT and ABMT treatment arms in the Schmitz trial (median follow-up 311 days) supports this assumption[6]. Moreover, our findings are in agreement with a retrospective study[7] which showed lower follow-up costs for PBSCT than for ABMT during the first month after discharge.

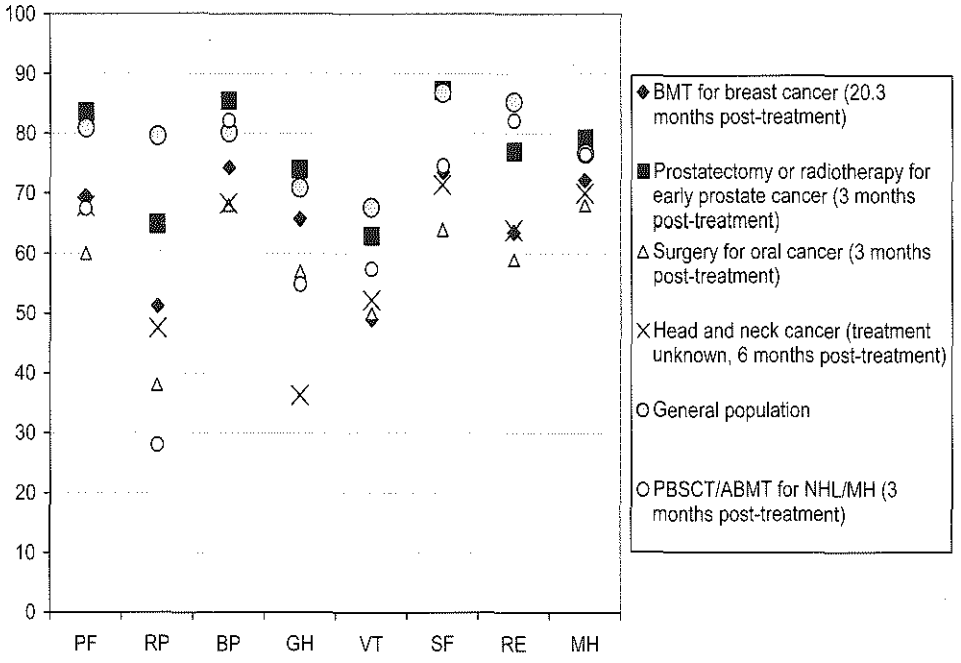
Although our sample size was relatively small, it is the largest sample of NHL and MH patients considered up until now in a prospective randomised trial. Moreover, in the current sample, important differences were already found in both treatment costs and in the cancer-specific RSCL quality of life measurements. It can be argued that in a larger sample significant differences would have been found using the generic EuroQol and SF-36 quality of life questionnaires, which would have made the results even more convincing, as generic questionnaires are less sensitive for changes in health states than disease-specific questionnaires like the RSCL. An indication for such differences can be found in the results on the EuroQol $5D_{index}$, which was considerably, but not significantly higher in the PBSCT arm 14 days after transplantation.

All cost-effectiveness analyses in PBSCT and ABMT trials so far have primarily used haematological outcomes as intermediate effect measures. Quality of life measurements have never before been made in the short term post-treatment comparison of patients having undergone either PBSCT or ABMT. The generic questionnaires used enable a comparison with other patient groups. For the SF-36 scores, we made such a comparison of the entire study group at 3 months after discharge to patients having undergone treatments for other neoplasms and to the general Dutch population with the same age distribution as our study group[24-28]. In this comparison (Figure 2), our study group has not been divided into the PBSCT/ABMT arms as no significant differences between these groups had emerged in the SF-36 analysis. Although most scores for the PBSCT/ABMT-treated patients are in the range seen for the other cancer patients, the score on the physical role functioning scale is extremely bad. On the contrary, the score on the emotional role functioning scale is better than in any other group of cancer patients. Except for these differences, it seems that the quality of life of patients having undergone PBSCT or ABMT for NHL/MH is not very different from the quality of life of other cancer patients.

Regarding the cost analysis, absolute comparisons to earlier studies cannot be made due to the different methodologies and assumptions[13] and large variations in unit costs between countries[29]. For a comprehensive comparison of cost analyses in PBSCT/ABMT, we refer to Waters and colleagues[14]. Disregarding the absolute costs reported, a similarity in all prospective and retrospective studies focusing on differences in costs between PBSCT and ABMT for lymphomas is the observation of a cost advantage for PBSCT treatment over ABMT, ranging from 15% to 30%[8-12, 31]. The relative cost advantage of PBSCT over ABMT in our analysis is 15%, or 21% if costs are considered from the harvesting phase onwards (as in most of the earlier studies).

To summarise, this study comprises the largest prospective randomised trial in patients with relapsed or refractory NHL/MH undergoing either PBSCT or ABMT treatment. The haematological outcomes are in accordance with earlier randomised clinical trials. Our study strongly confirms reports in the literature with a cost advantage for PBSCT treatment. In addition, it demonstrates a favourable quality of life for this arm indicating that PBSCT is the treatment of choice for patients with refractory or relapsed NHL/MH.

Figure 2. Comparison of the mean SF-36 scores in the entire study group (PBSCT + ABMT, n=91) to mean scores of the general Dutch population, which have been altered to resemble the age distribution of the study group[24]. Comparison to bone marrow transplantation (BMT) for breast cancer[25], to radical prostatectomy or radical external beam radiotherapy for early prostate cancer[26], to surgery for oral cancer[27] and to (unreported treatments in) head and neck cancer patients[28]. PF = Physical functioning, RP = Role funtioning-physical, BP = Bodily pain, GH = General health, VT = Vitality, SF = Social functioning, RE = Role functioning-emotional, MH = Mental health. 0 (worst) to 100 (best). PBSCT, peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation; NHL, non-Hodgkin's lymphoma; MH, Morbus Hodgkin.



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Chapter 6. A review of recruitment criteria, patient characteristics and results of CHOP chemotherapy in prospective randomized phase III clinical trials for aggressive non-Hodgkin's lymphoma

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Abstract

It has frequently been questioned whether results of trials can be generalized to routine clinical practice. Results obtained with standard cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy for aggressive non-Hodgkin's lymphoma in the control arm of prospective randomized phase III clinical trials during the past 25 years appear to be comparable. As the possibility to generalize trial results is favored by such consistency, we tested this hypothesis and tried to indicate explanatory 'moderator variables' (inclusion and exclusion criteria, therapy characteristics, sample sizes, inequalities in the distribution of patients over prognostic categories across different trials) in the case of divergent trial results. Trial results on conventional CHOP chemotherapy were obtained from literature research. Overall response (OR), complete response (CR) and two-year overall survival (2YS) were considered as outcome measures.

Although OR rates and 2YS rates were within acceptable limits of comparability, the absolute differences within the results were remarkably wide, particularly with regard to CR and 2YS. Divergent rates could not properly be explained by differences in the moderator variables. We conclude that absolute results obtained with CHOP in the control arm of trials appeared to be poorly generalizable to routine clinical practice, particularly in the case of elderly patients. This analysis underlines the need for the strict application of internationally agreed response criteria and the WHO classification system, large sample sizes and stratifying patients on the basis of prognostic factors, preferably in intergroup clinical trials. We expect those factors to lead to a better consistency of results in future trials and improved possibilities to generalize the results.

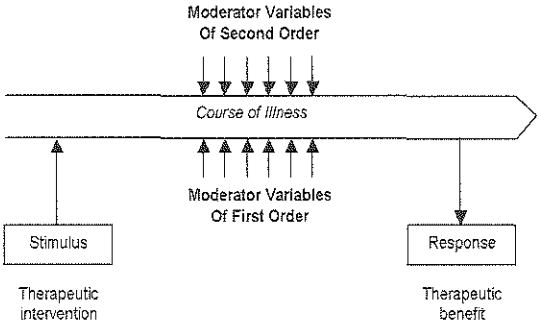
Introduction

Although clinical trials are conducted to improve patient care, it has been questioned whether results of prospective randomized phase III clinical trials can be generalized to the patient population seen in routine clinical practice[1]. Evidence from trials is sometimes even discarded because the patient sample is considered not to be representative for the results to be meaningful for generalization[2]. On the other hand, it has been argued that it is reasonable to generalize the results from trials[3], particularly when the intervention is mainly a biological process[4]. From a governmental or health insurance perspective, it is useful to know whether the *quantitative* result obtained in a clinical trial (for example, the absolute overall survival rate) can be generalized to routine clinical practice, particularly in the case of expensive treatments. For example, the cost-effectiveness ratio of a particular treatment is often mainly influenced by the treatment outcome.

For aggressive non-Hodgkin's lymphomas (NHL), the standard treatment has been CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy ever since McKelvey and colleagues demonstrated its superiority over COP (cyclophosphamide, vincristine, prednisone) chemotherapy in 1976[5]. Since then, CHOP chemotherapy has served as the control arm in many prospective randomized phase III clinical trials that were designed to demonstrate superiority of second- or third-generation chemotherapy schemes[6-33].

Regardless of the comparison of treatment arms within those trials, the results obtained with the standard CHOP arm in those trials appear to be more or less comparable at first sight. It would be important to test whether this is true, as the possibility to generalize trial results is favored by consistency between outcomes of those trials[34]. Nevertheless, it should be kept in mind that both patient- and physician-oriented factors may have caused differences between those trial outcomes. Winterer and Herrmann[35] have provided a clear model as a helpful tool in comparing outcomes of different trials on the one hand, and in assessing the possibility to generalize the therapeutic efficacy on the other hand (Figure 1). In spite of a comparable therapeutic intervention, therapeutic benefit observed within different trials may diverge as a consequence of the influence of so-called moderator variables of the first and second order. Most important in comparing results from different studies are the moderator variables of the first order: those variables able to cause differences between trial outcomes that were planned in advance. They mainly comprise the inclusion and exclusion criteria for patient recruitment. Moderator

Figure 1. Therapeutic efficacy (by Winterer and Herrmann[35]). Reprinted with the permission of Georg Thieme Verlag.



variables of the second order are the coincidental factors that might interfere with treatment (like environmental factors, daily clinical condition of the patient). Those are usually randomized and distributed equally in randomized trials.

We primarily evaluated the consistency of absolute treatment results obtained with standard CHOP chemotherapy for aggressive NHL within the control arm of prospective randomized phase III clinical trials. Our secondary aim was to assess whether differences between the trial results can be explained by differences in the predefined moderator variables of the first order (i.e., the inclusion and exclusion criteria of these trials) on the one hand, or an unequal distribution of the moderators of the second order on the other hand. This research was initiated to provide an indication of the extent to which the results of prospective randomized phase III clinical trials for aggressive NHL can be generalized to the patient population seen in routine clinical practice.

Materials and methods

Publications with results of randomized clinical trials for NHL were located by using the PubMed system and abstract books of the annual American Society of Hematology meetings. The following criteria were applied in order to select those publications to ensure that both patients and treatments included in our analysis were comparable as much as possible: (a) CHOP administered as first-line treatment, conventional CHOP scheme only (cyclophosphamide 750 mg/m^2 i.v., doxorubicin 50 mg/m^2 i.v., vincristine 1.4 mg/m^2 i.v. on day 1, prednisone given orally at days 1-5, all repeated at 21-day or 28-day intervals), (b) prospective randomized phase III clinical trials, (c) the majority of patients should have stage II-IV NHL (disseminated disease) according to the Ann-Arbor Staging System[36], as patients with stage I NHL (localized disease) are preferably offered limited chemotherapy followed by radiotherapy and have higher response rates[37]. No publications on low-grade lymphomas were included, because of the incurable nature of this type of NHL.

Only data from patients treated with standard CHOP in the control arm of the trials were considered. Patients receiving experimental treatments were excluded from analysis. Within the theoretical model of Winterer and Herrmann[35], we assumed the inclusion and exclusion criteria of the trials, the predefined therapy characteristics, and the number of patients aimed for to be the moderator variables of the first order. Moderator variables of the second order are coincidental factors which were not planned in advance and are frequently distributed equally between trial arms[35]. In our analysis, we considered the (in)comparability of the distribution of patients over favorable and unfavorable prognostic categories according to the International Prognostic Index[37] across the different trials to be the moderator variables of the second order, as these may be highly responsible for different trial outcomes. Unfortunately, the mean number of chemotherapy cycles actually delivered could not be used as a second order moderator variable, as this number has not been mentioned in all publications.

The overall response (OR) rate, the complete response (CR) rate and 2-year overall survival (2YS) were considered as the appropriate outcome measures (the 2YS rate was chosen as the survival outcome measure, because this was the only survival measure that was available from all selected publications). A final provision was therefore that both CR and partial response (PR) were reported in order to calculate OR. If the survival rate was not mentioned in the article text, it was estimated from the figures provided.

A weighted average of the outcome measures was calculated of the product of the number of patients treated with CHOP chemotherapy in each trial and the median age of those patients. The latter factor was applied to account for the fact that some of the trials were specifically targeted at elderly patients. Variations within the outcome measures were illustrated by using interquartile ranges, instead of confidence intervals. Confidence intervals as calculated on the available published data only (number of patients and the outcome measures) would have been too small as compared to a confidence interval calculated on the basis of the original data sets of the trials.

Table 1a. Inclusion criteria applied, as mentioned in the publications of the trials.

	Andersen 1980	Gordon 1992	Pavlovsky 1992	Fisher 1993	Cooper 1994	Bezwoda 1995	Sonneveld 1995	Zinzani 1995	Montserrat 1996	Tirelli 1998	Jerkeman 1999	Khaled 1999	Ezzat 2000	Giles 2000	Tilly 2000[a]	Freundschuh 2001	Coiffier 2002	Osby 2003	Doorduijn 2003
Single (S) or multicenter (M) trial	M	M	M	M	M	M	M	M	M	M	M	S	S	M	M	M	M	M	M
Inclusion criteria																			
Ann-Arbor stage I	-	-	-	-	B	-	-	-	-	-	X	X	X	-	X	X	-	-	-
Ann-Arbor stage II	-	-	B	B	X	X	B	X	X	X	X	X	X	X	X	X	X	X	X
Ann-Arbor stage III	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ann-Arbor stage IV	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ages included	≤75	all	≥16	all	>16	≥16	≥60	18-70	all	≥70	18-67	16-75	18-80	all	61-69	61-75	60-80	>60	≥65
CHOP cycle length (weeks)	4	3	3-4	3	3	3	4	3	3	3	3	3	3	4	3	3	3	3	3
CHOP no. of cycles aimed for	9	8	6	8	≥6	6-8	6-8	8-10	≥6	6	8	6	≥6	8	8	6	8	8	6-8

Table 1b. Exclusion criteria applied, as mentioned in the publications of the trials.

	Andersen 1990	Gordon 1992	Pavlovsky 1992	Fisher 1993	Cooper 1994	Bezwoda 1995	Sonneveld 1995	Zinzani 1995	Montserrat 1996	Tirelli 1998	Jerkeman 1999	Khaled 1999	Ezzat 2000	Giles 2000	Tilly 2000[a]	Pfreundschuh 2001	Coiffier 2002	Osby 2003	Doorduijn 2003
Exclusion criteria																			
Previous or other malignant disease	X			X		X	X				X			X	X		X	X	X
Concurrent serious illness, poor status					X									X			X	X	
Prior chemotherapy	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Prior (extensive) radiotherapy	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Prior organ transplantation															X				
Central nervous system involvement				X							X			X	[b]		X	X	
Bone marrow involvement												X							
Bone marrow involvement >25%																X			
Lymphoblastic lymphoma	X	X	X	X	X		X		X	X	X	X	X	X	[c]		X		X
Burkitt's lymphoma	X	X			X		X		X	X	X	X		X	[c]		X		
Performance score 3			X			X		X									X		
Performance score 4			X		X	X	X	X		X			X	X		X	X	X	
Hb <10.0 mg/dl														X					
WBC $\leq$3.0x10^9/l			X													X			
Absolute granulocyte count $\leq$1500/mm^3						X								X					
Absolute neutrophil count <1.0x10^9/l													X						
Platelet count $\leq$100x10^9/l			X			X							X	X		X			
Bilirubin $\leq$1.5x ULN			X											X					
Bilirubin >50 µmol/l																		X	
Creatinine clearance $\leq$60 ml/min			X	X		X													
Serum creatinine concentration HLA			2.0	1.7										1.7					
Serum creatinine >300 µmol/l																		X	
SGOT not above x times ULN						2								3				2.5	
SGPT not above x times ULN						2								3				2.5	
Alk. phosph. not above x times ULN						2												2.5	
Abnormal cardiac function			X	X		X	X	X	X	X		X		X	X	X	X	X	X
Abnormal hepatic function		X					X	X	X	X		X	X		X	X		X	X
Abnormal renal function		X					X	X	X	X		X	X		X	X		X	
Abnormal pulmonary function		X		X			X												
Neurologic contraindications																	X		
AIDS or known HIV infection				X			X	X	X					X	X		X	X	X
Unresolved Hepatitis B virus infection																	X		
Uncontrolled diabetes mellitus														X	X				
Active uncontrolled infection														X					
Active NM gastric or duodenal ulcer														X					
Severe autoimmune disease														X					
Thyroid function abnormalities														X					
Leptomeningeal lymphomatosis														X					
Pregnancy														X					

NM, not malignant; ULN, upper limit of normal level; HLA, highest level allowed; B, bulky localizations only. a: trial included patients with at least one adverse prognostic factor as defined by the age-adjusted IPI. b: in case of lymphoblastic or Burkitt's lymphoma, or primary cerebral lymphoma. c: only excluded in case of bone marrow or central nervous system involvement.

Results

Number of publications

In all, 29 publications on prospective randomized phase III clinical trials including CHOP chemotherapy for aggressive NHL were found. Nine publications were excluded for the following reasons: CHOP itself was experimental and followed by an irregular maintenance therapy[5], the trial included only patients with Stage I (localized) NHL[23], patients had low-grade NHL[9], a substantial part of the patient group had a systemic relapse following previous radiotherapy[7], only a favorable selection of patients was planned to receive full CHOP chemotherapy[18], irregular CHOP scheme or dosage[6, 20], no OR reported[8, 14]. Of two publications relating to the same trial, only the original article was used[15, 22]. In all, 19 publications were finally included in the analysis[10-13, 15-17, 19, 21, 24-33].

Inclusion and exclusion criteria (moderator variables of the first order)

Tables 1a / 1b presents an overview of the inclusion and exclusion criteria applied within the trials, as mentioned within the publications. Most of the trials included both intermediate and high-grade lymphomas[11-13, 15-17, 21, 24, 26-32]. One trial[19] only included intermediate-grade lymphomas, while three included high-grade lymphomas only[10, 25, 33]. Unfortunately, the histology classification systems applied differed, although in most publications the Working Formulation[38] was used[11-13, 15-17, 21, 24, 27, 28, 30]. In four trials[10, 19, 25, 33] the Kiel classification was applied[39], while in three[29, 32, 33] (also) the REAL classification was used[40]. In one publication[26], the classification system was not explicitly mentioned. Given these different histology classification systems applied, in Table 1b we choose to only present whether lymphoblastic or Burkitt's lymphomas were excluded or not.

Characteristics of the included patients (moderator variables of the second order)

Table 2 shows the characteristics of the patient groups, according to the five variables of the International Prognostic Index for aggressive lymphomas, which have been shown to be correlated to favorable versus unfavorable outcomes[37], respectively: age (≤60 versus >60), Ann-Arbor Stage (I/II versus III/IV), number of extranodal sites (≤1 versus >1), serum lactodehygrogenase (LDH) (≤1 times upper limit normal versus >1 times), performance status (0/1 versus 2-4).

Table 2. Characteristics of the included patient groups.

	Andersen 1990	Gordon 1992	Pavlovsky 1992	Fisher 1993	Cooper 1994	Bezwoda 1995	Sonneveld 1995	Zinzani 1995	Montserrat 1996	Tirelli 1998	Jerkeman 1999	Khaled 1999	Ezzat 2000	Giles 2000	Tilly 2000	Pfreundschuh 2001	Coiffier 2002	Osby 2003	Doorduijn 2003
Number of pts. treated with CHOP	44	174	44	225	111	132	72	52	76	60	192	40	51	215	312	152	197	104	152
Age (years)																			
Median	57		51[a]	56	53	54[a]	70	53	58	74	51	45	51	48	65	67	69	72	73
Lowest age included	32		19	15	16	19	60	26	21	70	18	19	18		61	61			65
Highest age included	73		75	79	72	81	82	69	82	93	67	75	78		69	75			90
Fraction below 60 years		0.49	0.73	[b]	0.62	0.60	0.00		0.41	0.00	0.80	0.83	0.67		0.00	0.00	0.00	0.00	0.00
Ann Arbor stages																			
I-II	-	-	0.23		0.41	0.20	0.21	0.16	0.29	0.38	0.50	0.35	0.49	0.29	0.19	0.45	0.20	0.38	0.28
III-IV	1.00	1.00	0.77		0.59	0.80	0.79	0.84	0.71	0.62	0.50	0.65	0.51	0.71	0.81	0.55	0.80	0.62	0.72
Number of extranodal sites																			
≤ 1		0.66	0.98		0.76	0.77			0.79						0.50	0.76	0.74	0.87	0.75
> 1		0.34	0.02		0.24	0.23			0.21						0.50	0.24	0.26	0.13	0.25
Serum lactodehydrogenase (LDH)																			
Normal		0.37	0.77	0.55	0.37		0.29		0.54		0.44		0.33		0.23	0.54	0.33	0.37	0.40
Elevated		0.63[c]	0.23[d]	0.45[d]	0.63[c]		0.71[d]		0.43[e]		0.56[d]		0.67[e]		0.77[c]	0.46[c]	0.67[d]	0.63[c]	0.60[e]
Performance status																			
0-1 (Ambulatory)	0.73	0.85	0.77		0.83	0.76	0.80		0.64				0.78	0.71	0.68	0.78	0.83	0.76	0.79
2-4 (Not ambulatory)	0.27[f]	0.15[g]	0.23[h]		0.17[g]	0.24[f]	0.20[f]		0.34[h]				0.22[g]	0.29[g]	0.32[a]	0.22[g]	0.17[g]	0.24[f]	0.20[f]
International Prognostic Index (IPI)[i]																			
IPI 0-2					0.62				0.58		0.80	0.68	0.43			0.54	0.47		0.43
IPI 3-5					0.38				0.39		0.17	0.32	0.57			0.46	0.53		0.55

a. Represents mean age.

b. 62% of patients <65 years of age.
c. Elevated LDH defined as >1x normal (or according to IPI[37]).
d. Elevated LDH defined as above 250 U/l.
e. Definition of elevated LDH unknown.
f. Performance status measured according to the WHO criteria.
g. Performance status measured according to the ECOG criteria.
h. Performance status measurement criteria not mentioned.
i. Represents the distribution on the standard IPI consisting of five prognostic factors. Data of trials that only presented the age-adjusted IPI have not been shown.

Therapeutic benefit

Table 3 shows the outcome data as presented in the 19 publications. Three publications did not describe the results of a part of their patients[13, 15, 21]. Therefore, in this comparison, the most valid way to calculate OR was to divide the number of responding patients by the total number of patients, including patients who were not evaluable and patients who died during treatment (mostly due to toxicity), despite the fact that some of the publications have left the latter patients out of consideration in their calculation of response. The resulting OR rates within the trials are shown in Figure 2. The horizontal line at 75% depicts the weighted mean OR rate of the trials, while the dotted lines at 69%

and 81% mark the weighted interquartile range (IQR). The CR rates (weighted mean 55%, IQR 53-63%) and the 2YS rates (weighted mean 59%, IQR 51-62%) are presented in Figures 3 and 4, respectively.

Table 3. Results obtained within the selected trials.

	Andersen 1990	Gordon 1992	Pavlovsky 1992	Fisher 1993	Cooper 1994	Bezwoda 1995	Sonneveld 1995	Zinzani 1995	Montserrat 1996	Tirelli 1998	Jerkeman 1999	Khaled 1999	Ezzat 2000	Giles 2000	Tilly 2000	Pfreundshuh 2001	Coiffier 2002	Osby 2003	Doorduijn 2003
Two-year overall survival (%)	61	59	58	62	57	56	51	92	58	65	70	82	71	71	51	60	57	57	47
Treatment result (no. of patients)																			
Response (complete + partial)	41	142	36	180	102	94	56	47	61	46	139	38	44	174	195	102	135	74	126
- complete response	30	88	31	99	65	73	35	33	42	27	72	27	41	118	168	96	124	61	81
- partial response	11	54	5	81	37	21	21	14	19	19	67	11	3	56	27	6	11	13	45
Failure, of which	3	32	8	45	9	38	15	5	15	14	53	2	7	41	117	50	62	30	26
- not evaluable	1	12	-	-	-	12	2	-	2	3	18	-	-	-	12	-	7	4	-
- stable or progressive disease	2	20	7	-	-	26	9	5		6	35	2	7	41	78	40	44	10	10
- death	-	-	1	2	5	-	4	-	2	5	-	-	-	-	27	10	11	11	16
- have not been described	-	-	-	43	4	-	-	-	11	-	-	-	-	-	-	-	-	5	-
Overall response rate	0.93	0.82	0.82	0.80	0.92	0.71	0.78	0.90	0.80	0.77	0.72	0.95	0.86	0.81	0.63	0.67	0.69	0.71	0.83
Complete response rate	0.68	0.51	0.70	0.44	0.59	0.55	0.49	0.63	0.55	0.45	0.38	0.68	0.80	0.55	0.54	0.63	0.63	0.59	0.53

Consistency assessment

Of the 19 trials, the OR rates of 12 trials are within the IQRs (Figure 2). We assumed the consistency of these 12 trials to be proper. The ORs obtained in the remaining seven trials are clearly outside the ranges. In Table 4, we present those first and second order moderator variables that *uniquely* distinguished those seven trials from the other trials (for example, cardiac dysfunction was not considered as an explanatory moderator variable, as the majority of trials applied this exclusion criterion). In case of empty columns, no proper explanations for the divergent results were found among the moderator variables.

With regard to the CR rates, nine out of 19 trials showed divergent results (Figure 3). The moderator variables uniquely distinguishing those trials from others are shown in Table 4. Seven out of 19 trials showed divergent 2YS rates (Figure 4). Their unique remarkable moderator variables are shown in Table 4.

Table 4. Moderator variables of the first and second order that may be responsible for the divergent OR, CR and 2YS rates observed.

	Andersen 1990	Cooper 1994	Zinzani 1995	Kloeker 1999	Ezzat 2000	Tilly 2000	Pfreundschuh 2001	Andersen 1990	Gordon 1992	Pavlovsky 1992	Fisher 1993	Spronk 1995	Tirelli 1998	Jerkeman 1999	Kloeker 1999	Ezzat 2000	Giles 2000	Pfreundschuh 2003
	--- Divergent overall response rate ---							------ Divergent complete response rate ------							---------- Divergent 2YS ----------			
First order moderator variables																		
High number of chemotherapy cycles aimed for	X		X					X										
Single-center trial				X	X										X			
Excluded patients with bone marrow involvement lymphoma				X											X			
Included patients with at least one adverse prognostic factor						X												
Small sample size (n<100)	X		X	X	X			X		X		X	X		X	X		
Second order moderator variables																		
High proportion of young patients		X		X	X					X				X	X	X		
High proportion of patients with ≤1 extranodal sites										X								
High proportion of patients with >1 extranodal sites						X			X									
High proportion of patients with normal LDH										X								
High proportion of patients with elevated LDH						X						X						
Trial's rate																		
Relatively higher (H) or low (L) as compared to other trials	H	H	H	H	H	L	L	H	L	H	L	L	L	H	H	H	H	L

a. The trial of Jerkeman and colleagues also had a high proportion of young patients. However, no attempt was made to explain the low CR rate in this trial by second order moderator variables, as this rate seems to have been highly influenced by the strict definition of CR in this trial, which –in contrast to many other trials– did not allow for any residual lesions.

Discussion

The consistency of the results obtained with standard CHOP chemotherapy for aggressive NHL in the control arms of 19 prospective randomized phase III clinical trials was assessed, under the hypothesis that a high consistency would favor the possibility to generalize the results. Secondly, following the theoretical model of therapeutic efficacy by Winterer and Herrmann[35], we tried to explain divergent trial results by differences within the predefined first order moderator variables (inclusion and exclusion criteria, predefined therapy characteristics, and the sample sizes aimed for) and inequalities in the final distribution of patients over (un)favorable prognostic categories across the different trials. Three outcome measures were considered: OR, CR, and 2YS. Although we preferred to have used a longer term survival measure, the majority of publications did not allow us to do so.

The *OR rates* of the 19 trials included varied from 63 to 95%. The results of 12 trials showed an acceptable consistency. First order and second order moderator variables that appeared to be reasonable explanatory variables of the divergent OR rates of the remaining seven trials are shown in Table 4. A high number of chemotherapy cycles aimed for appeared a unique first order moderator variable applied in trials with a high response rate. Also, high OR rates were shown in the two single-center trials[26, 27]. As institutional variation has been widely recognized in trials[41], the results of single-center trials may be assumed to be less generalizable. The trial with the highest OR rate in our comparison[26] had excluded patients with bone marrow involvement of lymphoma at forehand, which might be a plausible explanatory variable of this high OR rate obtained.

The trial with the lowest OR rate only included patients with at least one adverse prognostic factor[32]. Among the second order moderator variables, a high proportion of young patients and a high proportion of patients within unfavorable prognostic categories might have been explanations for relatively high[15, 26, 27] or low[32] OR rates. Nevertheless, the first order moderator variable 'small sample size' has probably been an important explanatory variable for a divergent OR rate, as four out of five trials with a relative high response rate had only included limited patient numbers (<100 patients).

With regard to the *CR rates*, the variation was even wider (running from 38 to 80%). Similar to the OR rates, the first order variables 'high number of cycles aimed for', 'single-center trial', and 'exclusion of patients with bone marrow involvement of lymphoma' appeared to be reasonable explanatory variables for a relatively high CR rate in three trials[10, 26, 27]. Again, 'small sample size' was the most frequently observed first order moderator variable. We found a few second order moderator variables (high proportion of young patients and high proportion of patients in (un)favorable prognostic categories) that might have led to the divergent CR rates observed in five trials[11, 12, 17, 26, 27]. Unfortunately, the publication of the Fisher trial[13] provided only a few data on what we have called second order moderator variables. In the end, we found no first or second order moderator variable that might have been an explanation for the low CR rate in the trials of Jerkeman and colleagues[25] and Fisher and colleagues[13]. The apparent strict definition of CR in the trial of Jerkeman (not shown) that did not allow for any residual lesions may be the only possible explanation for the lowest CR rate found in this analysis (38%). On the contrary, the French trial with its 63% CR rate[29] considered patients with persistent radiological abnormalities that had regressed in size by at least 75% to be complete responders ('unconfirmed CR'). These examples led us to an attempt to present an overview of the

Figure 2. OR rates of first-line CHOP chemotherapy for NHL within prospective randomized phase III clinical trials.

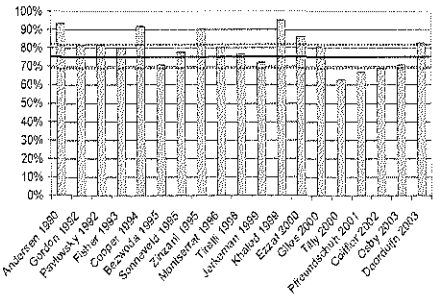


Figure 3. CR rates of first-line CHOP chemotherapy for NHL within prospective randomized phase III clinical trials.

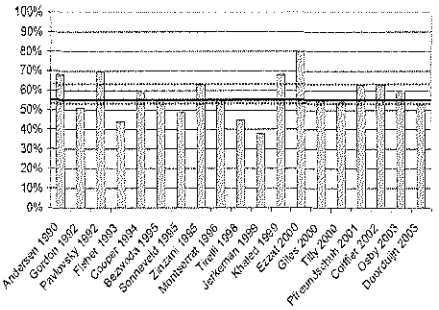
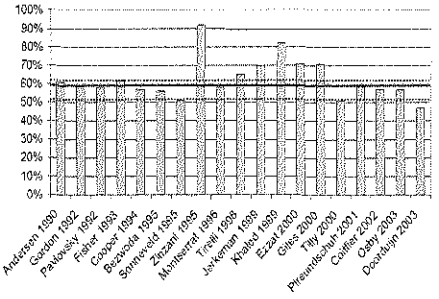


Figure 4. The 2YS rates of first-line CHOP chemotherapy for NHL within prospective randomized phase III clinical trials.



definitions of CR applied in the 19 trials. However, we finally decided not to show this overview given the low informative value. Although the majority of definitions are highly comparable, almost all leave room for some subjective adoption in clinical practice. This illustrates the need for international acceptance and application of criteria for response evaluation on which consensus has already been reached[42], as for example had already been applied in the French trial[29].

With regard to the *2YS rates* (ranging from 47 to 92%, Figure 4), seven out of 19 trials were outside the IQRs. The same first order moderator variables that were used in trying to explain divergent OR and CR rates may have been responsible for some divergent results. Among second order moderator variables, the only plausible variable found was a high proportion of young patients. No first or second order moderator variables were found that were helpful in explaining the relatively high and low 2YS rates of Giles and colleagues[28] and Doorduijn and colleagues[30], respectively. The fact that the latter trial focused on elderly patients could not be used as a unique variable, as the trial of Tirelli and colleagues[24] also focused on elderly patients, but nevertheless showed a relatively high 2YS rate.

With regard to the OR, CR and 2YS rates, Figures 2-4 show that the results of approximately one-half to two-thirds of the trials are within the IQRs. However, neither the divergent OR and CR rates, nor the divergent 2YS rates can actually unanimously be explained by the first and second order moderator variables. Notwithstanding this observation, Table 4 shows that the likelihood of divergent results is highly increased in case only limited patient numbers are included in trials. All but one of the eight trials that only included less than 100 patients show up at least once in Figures 2-4.

Although most of the trials were within the limits of comparability with regard to 2YS rates, the highest rate obtained was almost twice the lowest, which is at least a remarkable finding for this definite outcome measure. We postulate that this implies that the absolute results obtained with standard CHOP in these trials cannot be generalized well to the population seen in routine clinical practice. This may also be due to the immeasurable influence of the ever increasing understanding that NHL consists of a large number of different entities with different prognostic profiles. Although it seems highly probable that all trials have mainly been based on patients with diffuse large B-cell lymphoma, this observation might particularly have influenced older trials, as ameliorated technical possibilities to specify these subentities, and the consequent new WHO histology classification system[43] have only been developed within the past few years.

The assumed poor possibility to generalize the trial results in this patient group appears to be particularly true for the elderly patients. The most common exclusion criteria (poor performance status; cardiac, hepatic, or renal dysfunction; previous or concurrent malignant disease, for which prior therapy may have been administered) are likely to exclude far more elderly patients than younger patients. Support for this conclusion comes from a 1999 Dutch study on the presence of comorbidity in a population-based series of patients with NHL[44]. The prevalence of comorbidity was 61% in patients aged $\geq$ 70 years, chemotherapy turned out to be administered less often to elderly patients and the overall survival was lower in the case of comorbidity. Other studies in elderly NHL patients had also shown a frequent occurrence of incomplete staging and inadequate treatment, or the administration of

reduced dose treatments[45-48]. A comparison of elderly patients with aggressive lymphomas who were entered or not entered into a randomized phase II trial showed that non-randomized patients had a poorer performance status, were less likely to be given treatment with curative intent, and were less likely to complete the full number of projected treatment courses[49]. In the above-mentioned Dutch study, 80% of the NHL patients under the age of 60 years had no comorbidity at all[44]. This would imply that the results obtained in trials might in theory be realized in the vast majority of younger NHL patients treated outside trials, particularly because none of the common exclusion criteria are likely to exclude many younger patients. Indications for the potential truth of this assumption come from a recent study in patients with Hodgkin's lymphoma that demonstrated identical 10-year relative survival rates in trials and population-based series at ages under 45 years[50]. However, in patients aged 65 years and above, the survival was higher in patients included in clinical trials. This may again have been due to the higher rate of 'noneligibility' of elderly patients. In other diseases, similar conclusions were drawn[51, 52]. On the contrary, in a comparison of a population-based registry of children with acute lymphoblastic leukemia diagnosed and treated in Britain throughout 1971-1984, a higher survival rate was found for patients included in the Medical Research Council trials[53]. Identically, a higher survival rate was found for patients with Hodgkin's lymphoma treated by American comprehensive cancer centers as compared to the survival of patients in a population-based registry[54]. Although this may lead to the assumption that the treatment center has an influence on the treatment outcome, it has also been shown that within oncology trials, small community hospitals are able to generate treatment outcomes similar to the results obtained within large university hospitals[53, 55-58]. It is therefore more plausible that a difference in experience has influenced the relative favorable survival within specific hospitals, as it has been recognized that only a selection of hospitals participate in clinical trials[1, 59]. Some older evidence exists on the capability of specialist centers to produce better treatment outcomes[53, 60, 61]. In theory, this finding would be rather encouraging for the possibility to generalize results obtained in trials on first-line CHOP chemotherapy for NHL, as this treatment can be administered in general hospitals and does not call upon the level of specialist experience required for more intensive treatment modalities, like stem cell transplantation. Therefore, CHOP is widely regarded as the treatment of first choice for newly diagnosed aggressive NHL[62]. A prerequisite for obtaining routine clinical practice results similar to those reported in trials is adherence to the treatment protocol. If possible, a full course of chemotherapy should be applied and doses should be reduced as little as possible[63]. The positive message from this analysis is that patient survival may be better when patients are treated according to standard protocols[64] and that protocol-defined treatment schedules may lead to better results[65].

Finally, it has been questioned whether the absolute quantitative result obtained in a clinical trial should be generalized at all[66, 67]. Besides the importance to clinical practice, the importance is a policy-related one. The cost-effectiveness of healthcare interventions will improve by identifying those patients in whom a specific treatment is ineffective and those patients who are most likely to benefit[68]. For the practice of effective health policy, information needs to be available on the cost-effectiveness

of medical treatments. These ratios are often more sensitive to the value of the outcome measure than to the costs of treatment.

Although our study lacks the power of a meta-analysis, it clearly demonstrates the need for highly detailed presentations of exclusion criteria, patient characteristics and outcomes of clinical trials, if the publications of these trials are to be used for improving patient care or making health policy decisions. The development of clinical practice guidelines underlines this argument as recommendations in those guidelines are usually based on the results from literature research ('evidence-based medicine').

Conclusion. Randomized trials have a high internal validity and therefore are highly useful to demonstrate differences between treatment modalities. However, from this analysis, the external validity of the absolute trial results appears to be low. Using the published information so far available on CHOP administered as first-line chemotherapy for aggressive NHL within prospective randomized phase III clinical trials, we assume to have indicated a poor possibility to generalize the absolute trial results. This is at least a disappointing result for a treatment that has been a standard treatment for over 25 years. Reaching international consensus about the strict application of agreed response criteria and the WHO histology classification system, the inclusion of large patients numbers and stratifying them on the basis of prognostic factors (like those of the International Prognostic Index[37]), preferably in international cooperative group trials, appear to have the potential to result in a higher consistency of trial outcomes. It seems plausible that applying this will lead to a better representativeness of large multicenter trials for routine clinical practie, or, in other words, to ameliorated possibilities for generalization of trial results.

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Chapter 7. Survival of patients with aggressive non-Hodgkin's lymphoma: no difference between first-line treatment in a prospective randomised phase III clinical trial and first-line treatment according to routine clinical practice

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Abstract

Objective. To compare survival of patients with disseminated aggressive NHL who were treated either as part of a clinical trial or in routine clinical practice.

Design. Retrospective.

Method. The survival was studied of patients with disseminated NHL of intermediate or high grade malignancy who were treated in the Meander Medical Centre, Amersfoort, The Netherlands, in the years 1994-2001 with chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). This took place either in routine clinical practice (RCP) or as part of a clinical trial where patients <65 years of age received intensified CHOP and patients >65 years received CHOP with growth factors. Treatment data, the response to therapy, survival and prognostic factors according to the International Prognostic Index for aggressive NHL were collected by a review of the patient records.

Results. Fifty-nine patients were eligible for this analysis: 32 men and 27 women with a median age of 63 years (range 30-83). Of these, 35 were treated within a clinical trial and 24 in RCP. There was no difference in median survival between the trial and RCP groups, this being 27 months for all patients, 34 months for the younger patients, 20 months for the elderly patients, and 42 months for patients who achieved complete remission following chemotherapy.

Conclusion. No difference in overall survival was found between patients with disseminated aggressive NHL who underwent treatment according to either RCP or as part of a clinical trial. It demonstrates that both patients in clinical trials and patients treated according to RCP received equally effective therapy. Recent developments in NHL treatments are promising, and therefore participation in clinical trials should be encouraged.

Introduction

Since 1976, the standard first-line treatment for aggressive non-Hodgkin's lymphoma (NHL) has been CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy[1, 2]. From that year onwards, almost 30 prospective randomised phase III clinical trials were performed in order to develop superior treatment schemes, thus far without success[3].

In the Meander Medical Centre in Amersfoort, it has been standard practice since 1994 to treat NHL patients in clinical trials from the Dutch Working Group on Adult Haemato-Oncology (HOVON) if possible, in case of eligibility and informed consent. The two most important HOVON trials on first-line treatment of NHL in the recent decade were the HOVON-25 trial for elderly patients (≥65 years) and the HOVON-26 trial for younger patients (<65 years). The HOVON-25 (which has been completed in the meantime) compared the standard CHOP treatment to the same treatment to which prophylactic haematopoietic growth factors (granulocyte colony-stimulating factor, G-CSF) were administered at each cycle. The assumption was that severity and duration of leukopenia and consequent infections, which often occur in elderly patients, could be reduced by prophylactic G-CSF administration[4]. Moreover, dose reduction of the chemotherapy might be prevented, possibly resulting in higher chances of reaching complete remissions[5]. The HOVON-26 trial (still open for inclusion) compares the standard CHOP treatment to the same treatment administered in a more intensive scheme (6 times CHOP at higher doses, administered at 14-day intervals, with G-CSF support), under the hypothesis that exposing tumour cells to maximum tolerated doses within shorter time intervals between the cycles might circumvent the problem of chemotherapy resistance[6].

It has frequently been stated that results obtained in daily local practice might not always be comparable to the 'ideal situations' in clinical trials, in which stringent inclusion and exclusion criteria are applied[7-10]. Therefore, after eight years of trial participation, we compared the results of our trial treated patients to the results obtained in our patients who were not treated according to trial protocols.

Methods

For this retrospective analysis, the Regional Cancer Centre Mid-Netherlands identified all patients who were diagnosed with NHL between 1 January 1994 and 31 December 2001 in the Meander Medical Centre. In this time interval, we tried to offer all eligible NHL patients a treatment within a randomised clinical trial (RCT). Patients were included in the comparison in case of treatment according to the HOVON-25 or HOVON-26 protocol or similar patients who received standard CHOP chemotherapy outside RCT context (cyclophosphamide 750 mg/m^2 iv, adriamycine 50 mg/m^2 iv, vincristine 1.4 mg/m^2 iv on day 1, prednisone orally on days 1-5; in total 6 to 8 times with 21-day intervals). This implies that in these trials and therefore in this analysis only patients with Ann-Arbor stage II-IV NHL (disseminated

disease) of intermediate or high-grade malignancy (aggressive NHL) according to the Working Formulation were included[11]. (Currently, generally the 'Revised European-American classification of lymphoid neoplasms' (REAL) is used, which distinguishes lymphomas on the basis of morphologic, immunologic, cytogenetic, and molecular-biologic characteristics[12]. For a comparison of both classification systems we refer to an earlier article in this journal[2]. In 2001 a WHO classification was published, which is actually a refined version of the REAL classification[13, 14]). Patients who did not undergo treatment or who received treatment elsewhere were left out of consideration.

Gender, therapy response, survival and the five variables of the International Prognostic Index for Aggressive NHL were mapped by chart review[15]. In this index the following favourable versus unfavourable variables are included: age ≤60 years vs. >60 years, Ann-Arbor stage I/II vs. III/IV, serum LDH normal vs. elevated (≥2x upper limit of normal value), performance status 0/1 (ambulatory) vs. 2-4 (not ambulatory), number of extranodal sites ≤1 vs. >1. For each unfavourable variable, one point is calculated, from which the following prognostic risk profile is obtained: low (0-1), low-intermediate (2), high-intermediate (3), high (4-5).

Response was categorised into the standard classes of complete remission, partial remission, stable disease, and progressive disease (see guidelines of the HOVON for extensive definitions of therapy response: www.hovon.nl).

Statistical analysis was performed using SPSS for Windows version 10.0. Patient characteristics were compared by the χ^2 test for categorical variables and the T-test for continuous variables (age). Survival was calculated by means of Kaplan-Meier survival curves and was compared by the log-rank test. Median survival was calculated by the life-tables procedure. A significance level of 0.05 was used. Missing values were left out of consideration in the calculation of percentages.

Results

On the basis of the cancer registration, 79 patients were found in the interval 1994-2001. Twenty of them were not included in the analysis because of the following reasons: no treatment in consultation with the patient, for example because of high age or co-morbidity (10), patient underwent treatment elsewhere (3), NHL found post-mortem at autopsy (4), other type of lymphoma (3). Of the 59 included patients, 35 underwent treatment within the HOVON-25 or HOVON-26 trial, and 24 received standard treatment not in the context of a clinical trial. Reasons why patients were not included in a clinical trial were: treatment before the trial was open for inclusion (4), patient refusal (6), no participation offered (1), not eligible because of exclusion criteria present: serum LDH too high (3), performance status too poor (2), histology not conclusive (1), previous malignancy (2), Alzheimer's disease (1), cardiac status insufficient (1), severe COPD (1), inadequate renal function (1), liver cirrhosis (1). Characteristics of the included patients are shown in Table 1. The groups did not differ from each other, except for the higher mean age of patients treated in a trial amongst the elderly patients (P=0.036).

Table 1. Characteristics of 59 (%) patients with disseminated aggressive NHL, treated in 1994-2001 within or without a trial protocol in the Meander Medical Centre Amersfoort. IPI = International Prognostic Index[15].

	Entire group		Patients ≤ 60 years		Patients > 60 years	
	no trial	trial	no trial	trial	no trial	trial
n	24	35	9	17	15	18
Gender:						
- male	14 (58)	18 (51)	7 (78)	8 (47)	7 (47)	10 (56)
- female	10 (42)	17 (49)	2 (22)	9 (53)	8 (53)	8 (44)
Age:						
- mean	63.8	62.3	54.3	49.8	69.4	74.2
- median	62.5	63.0	57.0	52.0	70.0	76.0
- range	35-80	30-83	35-60	30-59	62-80	63-83
Age (IPI):						
- ≤ 60 years	9 (38)	17 (49)	9 (100)	17 (100)	-	-
- > 60 years	15 (62)	18 (51)	-	-	15 (100)	18 (100)
Ann-Arbor stage:						
- II	8 (35)	6 (18)	5 (56)	3 (19)	3 (21)	3 (17)
- III / IV	15 (65)	28 (82)	4 (44)	13 (81)	11 (79)	15 (83)
- unknown	1	1	-	1	1	-
Serum LDH:						
- normal	17 (81)	27 (79)	8 (89)	13 (81)	9 (75)	14 (78)
- elevated	4 (19)	7 (21)	1 (11)	3 (19)	3 (25)	4 (22)
- unknown	3	1	-	1	3	-
Performance status:						
- ambulatory	22 (100)	31 (97)	9 (100)	14 (93)	13 (100)	17 (100)
- not ambulatory	-	1 (3)	-	1 (7)	-	-
- unknown	2	3	-	2	2	1
Extranodal localisations:						
- ≤ 1	18 (78)	25 (73)	9 (100)	11 (69)	9 (64)	14 (78)
- > 1	5 (22)	9 (27)	-	5 (31)	5 (36)	4 (22)
- unknown	1	1	-	1	1	-
IPI risk profile:						
- low	11 (52)	13 (41)	9 (100)	10 (67)	2 (17)	3 (18)
- low-intermediate	5 (24)	13 (41)	-	4 (27)	5 (42)	9 (53)
- high-intermediate	2 (10)	3 (9)	-	1 (7)	2 (17)	2 (12)
- high	3 (14)	3 (9)	-	-	3 (25)	3 (18)
- unknown	3	3	-	2	3	1

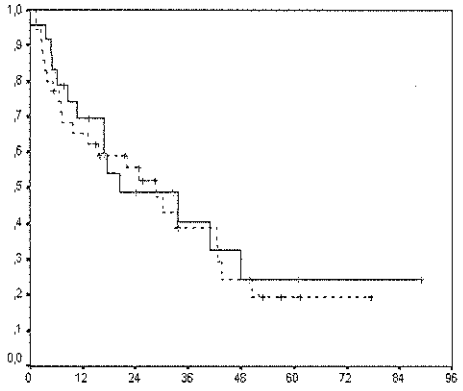
Table 2 presents the results of the first-line treatment. The category 'not-evaluable' contained patients who died during or shortly after treatment, in whom restaging procedures were not performed yet.

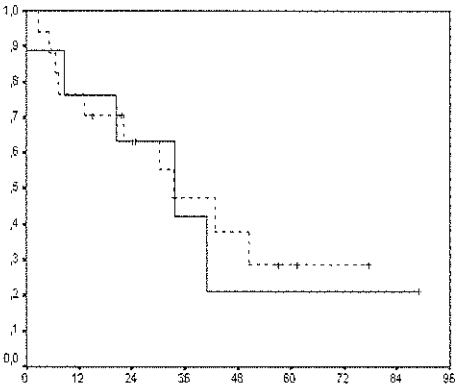
Table 6. Results of the first-line treatment of 59 (%) patients with disseminated aggressive NHL who were treated in 1994-2001 within or without a trial protocol in the Meander Medical Centre Amersfoort.

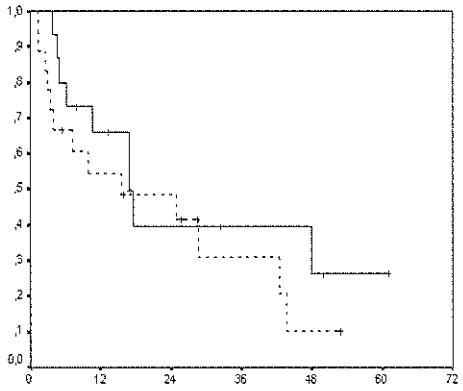
	Entire group		Patients ≤ 60 years		Patients > 60 years	
	no trial	trial	no trial	trial	no trial	trial
Complete remission	13 (54)	18 (51)	7 (78)	8 (47)	6 (40)	10 (56)
Partial remission	4 (17)	7 (20)	-	6 (35)	4 (27)	1 (6)
Stable disease	1 (4)	2 (6)	-	-	1 (7)	2 (11)
Progression	1 (4)	2 (6)	1 (11)	2 (12)	-	-
Not evaluable	5 (21)	6 (17)	1 (11)	1 (6)	4 (27)	5 (28)

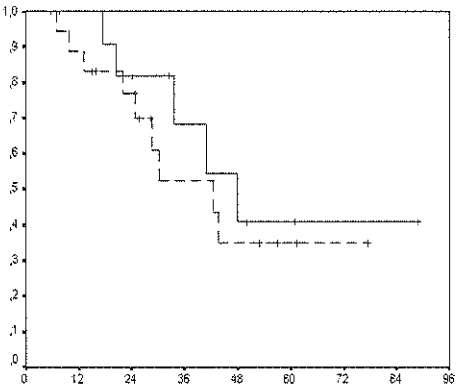
Survival is shown in Figures 1 (entire group, P=0.79), 2 (younger patients, P=0.80), 3 (elderly patients, P=0.34), and 4 (patients who reached complete remission after first-line treatment, P=0.53). None of these survival curves showed significant differences between patients who were treated in a clinical trial and patients who received standard treatment according to routine clinical practice. Therefore, median survival was calculated without this distinction: 27.3 months (entire group), 34.3 months (younger patients), 19.8 months (elderly patients), and 42.1 months (patients who reached complete remission).

Figures 1 (upper left), survival entire non-trial group (solid line, n=24) versus entire trial group (dashed line, n=35); 2 (upper right), survival of younger non-trial patients (solid line, n=9) versus younger trial patients (dashed line, n=17); 3 (lower left), survival of elderly non-trial patients (solid line, n=15) versus elderly trial patients (dashed line, n=18); 4 (lower right), survival of patients who reached complete remission, non-trial group (solid line, n=13) versus trial group (dashed line, n=18).









Discussion

In this study, the survival of patients with disseminated aggressive NHL who received standard CHOP chemotherapy was compared to the survival of similar patients who were treated in a clinical trial by means of the same treatment or the treatment under study (intensive CHOP for younger patients and CHOP with haematopoietic growth factors in elderly patients). No survival differences were shown between the groups (provided that patients underwent treatment) and survival was concluded to be identical (Figures 1-4). Although this result was only based on small patient groups from one hospital, this is in principle an important result for the individual patient with NHL, because it demonstrates that both patients who were treated in a trial as well as patients who were treated according to standard practice received equally effective care. As was expected, the median survival of NHL patients who reached complete remission in both groups turned out to be significantly higher than the survival of the other patients (Figure 4). This emphasises the importance of trying as much as possible to induce complete remissions in these patients[5].

Of course, this conclusion can not be generalised without restrictions to other types of patients, and our analysis only allows for conclusions regarding patients with aggressive NHL. Moreover, our conclusion only applies to patients who actually received treatment: 10 patients who had an 'eligible type' of NHL were excluded from our analysis, because they did not undergo treatment.

Little is known about the quality of care outside the context of clinical trials[10]. Therefore, there is not much comparable literature available. With regard to haematological malignancies, only one study addressing a similar question was found. A study in patients with Hodgkin's lymphoma showed 10-year survival of patients <45 years treated in clinical trials to be identical to the survival of all known patients <45 years[16]. However, treatment results in Hodgkin's lymphoma are on average always better than treatment results in NHL, also in case of non-trial treatments. Survival of patients >65 years was better in case of trial treatment[16]. This may have possibly been due to the high incidence of co-morbidity in elderly patients, which often serves as an exclusion criterion for trial participation. With regard to NHL, a Dutch study showed that 61% of the patients >70 years suffers from co-morbidity, whereas 80% of the patients <60 years did not suffer from any co-morbidity[17]. Also, it was shown that in elderly NHL patients, fewer chemotherapy cycles are often administered and in lower doses, despite the fact that this is strongly discouraged in case of curative treatment[5, 17-21]. An earlier Dutch study showed the lack of flagrancy regarding delay of chemotherapy cycles or dose reduction in daily clinical practice[1]. In this respect, protocol treatments offer more guidance than non-protocol treatments, because in clinical trials stringent rules are often applied in this area. Furthermore, it is not impossible that the stringent dose discipline applied in our centre (also in case of non-trial treatments) helped to realise the comparable results within this analysis.

The results of our analysis correspond with the results obtained with CHOP chemotherapy in the past 25 years. The HOVON-25 trial also did not show survival differences between patients who received standard CHOP and patients who received the study therapy[4]. The section of Figure 3 that is based

on a reasonable number of patients (until approximately 24 months) shows a proper comparability to the results of the entire HOVON-25 trial[4].

In summary, in a hospital with a tradition of protocol medicine, no obvious differences were shown between the survival of patients treated within or outside the context of clinical trials. Nevertheless, participation in clinical trials should be encouraged as much as possible. Although the standard therapy for patients with disseminated aggressive NHL has not changed for a long time as a result of clinical trials, short-term perspectives are promising. For our hospital, the possible improvement of the standard therapy and the results of this analysis are adequate reasons to continue stimulating participation in clinical trials, given the arguments reflected above.

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Chapter 8. CHOP chemotherapy for aggressive non-Hodgkin's lymphoma: cost-efficacy versus cost-effectiveness

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Submitted.

Abstract

We investigated if cost-effectiveness results of first-line CHOP chemotherapy for non-Hodgkin's lymphoma (NHL) obtained in randomised clinical trials (RCTs) may be representative of standard local practice (SLP).

Data of aggressive NHL patients stage II-IV having received CHOP according to RCT or SLP were collected retrospectively. Costs were calculated from the hospital perspective. Main outcome measure: costs without haematopoietic growth factors, as half of the RCT patients received these by design.

374 patients were included. Base case analysis: total costs were equal among RCT and SLP in younger patients (≤60 years), but in elderly patients (>60 years), RCT patients had higher costs. In matched pairs analyses (MPA), this cost difference decreased to only 11-13%. Survival analyses also showed no difference between RCT and SLP occurred.

Given the similar survival and comparable costs, we conclude that cost-effectiveness results obtained in RCTs on first-line treatment for aggressive NHL may be representative of SLP.

Introduction

It has been questioned whether results of randomised clinical trials (RCTs) can be generalised to the patient population seen in routine clinical practice[1]. Nevertheless, RCT results usually constitute the foundation for clinical practice guidelines and in this respect, RCT results are in fact considered to be representative of daily practice. A similar reasoning is true for cost-effectiveness analyses piggybacked to RCTs. However, if costs and/or effects of the experimental arm and the standard arm have been overestimated or underestimated, the cost-effectiveness ratio may not be reflecting reality.

Of all haematological malignancies, Non-Hodgkin's lymphoma (NHL) has the highest incidence rate[2]. The majority of NHL patients suffer from the aggressive subtype, for which standard first-line therapy has been CHOP (cyclophosphamide, adriamycine, vincristine, prednisone) chemotherapy since 1976[3, 4]. Patients with disseminated disease (stage II-IV) will receive 6-8 CHOP cycles, resulting in a 5-year overall survival rate of approximately 50%, varying from 25% to 75%, depending on the risk factors at diagnosis[5]. In a survey on diagnosis and treatment of NHL in the Netherlands, all haematologists said to apply this standard CHOP chemotherapy (with 21-days cycle intervals) in the case the patient is not treated within an RCT[6]. Since 1976, many NHL patients were treated in RCTs worldwide, as almost 30 RCTs were performed trying to develop superior treatment schemes to CHOP[3]. Economic evaluations were conducted alongside several of them. However, it has never been investigated if cost-effectiveness as established in NHL RCTs ('cost-efficacy') may be representative of cost-effectiveness in daily clinical practice. Only one study suggested that costs of CHOP within RCTs might be comparable to CHOP applied in daily clinical practice, but this study was based on small patient numbers[7].

In this study, it was investigated if cost-efficacy data from RCTs in patients with stage II-IV undergoing CHOP first-line chemotherapy for aggressive NHL may be representative of cost-effectiveness results obtained in daily clinical practice.

Patients and Methods

Patient groups

This study compared patients who received first-line CHOP chemotherapy in an RCT with patients who received CHOP according to standard local practice (SLP). Following international recommendations, two age groups were defined: younger (YNG, ≤60 years) vs. elderly (ELD, >60 years) patients[5]. So, 4 groups of patients served as the basis for this analysis: RCT-YNG, RCT-ELD, SLP-YNG, and SLP-ELD.

For elderly RCT patients (RCT-ELD), data were used from the HOVON (Dutch Working Group on Adult Haemato-Oncology) NHL-25 trial, comparing CHOP with CHOP combined with prophylactic administration of granulocyte colony-stimulating factor (G-CSF)[8]. Inclusion criteria were: ≥65 years, stage II-IV, newly diagnosed aggressive (intermediate or high-grade malignancy) NHL[9, 10]. Exclusion

criteria were: lymphoblastic NHL, positive HIV serology, concurrent or previous malignancy except localised squamous skin carcinoma, severe cardiac disease, abnormal liver or kidney function unless caused by NHL, or CNS (central nervous system) involvement. A cost-effectiveness analysis was piggybacked to this RCT, performed by our group, from which cost data of a random selection of 100 of all 389 patients were available.

For the other groups (RCT-YNG, SLP-YNG, SLP-ELD), patients treated between 1993 and 2001 were randomly selected from registries by haematologists from 15 hospitals (11 local, 4 university hospitals). The aim was to include approximately 100 patients in all groups (number set by practical considerations).

For the younger RCT patients (RCT-YNG), data were used of patients from the HOVON NHL-26 trial, comparing 8x standard CHOP every 21 days with 6x intensified (14-days cycle interval, higher cyclophosphamide and doxorubicin doses) CHOP+G-CSF. Scheduled total doses of cyclophosphamide and doxorubicin were equal in both arms. Inclusion criteria were: 15-65 years (some of these patients might therefore have been included in the RCT-ELD group of this analysis), newly diagnosed aggressive stage II-IV NHL. Exclusion criteria were: lymphoblastic NHL, positive HIV serology, other or previous malignancy except stage I cervix carcinoma or basocellular carcinoma, severe cardiac, pulmonary, neurologic or metabolic disease, abnormal liver or kidney function unless caused by NHL, or CNS involvement.

In the RCT groups, patients from both the experimental and the standard arms were included.

Patients in the two SLP groups (SLP-YNG/SLP-ELD) were selected in the case of newly diagnosed aggressive stage II-IV NHL, and treatment with standard CHOP (cyclophosphamide iv 750 mg/m^2 day 1, adriamycin iv 50 mg/m^2 day 1, vincristine iv 1.4 mg/m^2 (max. 2 mg) day 1, prednisone orally 100 mg days 1-5, repeated at 21-days intervals), not administered according to an RCT protocol. Patients with lymphoblastic lymphomas were not included because of a greatly different prognosis. No further exclusion criteria were applied, in order to attain a population-based sample of CHOP treated stage II-IV aggressive NHL patients.

Cost analysis

Costs were calculated from the date the first-line treatment was started, up to 10 days after the end of the last cycle. The main outcome measure was 'total cost excluding G-CSF'. Given the design of the 2 RCTs, the total costs including G-CSF would have been higher in the trial groups at forehand, which would impede a proper comparison of the remaining cost items. Costs including G-CSF are presented for informative reasons. The cost analysis was performed according to the hospital perspective, and was therefore based on all medical resource use generated within the hospital in the analysis time frame, which data were collected from anonymous databases, generated by the administrative departments of the hospitals. Drug use at home was also estimated from notes in patient files. Resource use for co-morbidity was not recorded. For the valuation of the most important items within the resource use, separate unit costs were calculated (price level 2000) reflecting full hospital costs[11,

[12]. To determine these unit costs, we applied the micro-costing method, which is based on a detailed inventory and measurement of resources consumed[13]. Unit costs as calculated on the basis of financial data from five of the participating hospitals were: inpatient hospital day €318 of which 57% personnel costs (P), 14% material costs (M), and 29% overhead costs (O); haematology outpatient visit €61 of which P 80%, M 4%, O 16%; other outpatient visit €55 of which P 80%, M 4%, O 16%; use of day care ward €142 of which P 44%, M 18%, O 38%; radiotherapy megavolt session €191 of which P 62%, M 15%, O 23%; lymph node biopsy under general anaesthesia €555, of which P 46%, M 31%, O 23%. For items with low costs or minor influence (due to low average numbers), Dutch tariffs were used as approximations. Costs of medication were based on Dutch wholesale prices[14].

Survival analysis

For this analysis, patients were followed-up as long as possible (last date available up to the last date of data collection in June 2002). The overall survival (OS) time was calculated from the start of the first-line treatment onwards. Event-free survival (EFS) was measured from the start of the first-line treatment until no complete remission (CR) or partial remission (PR) was recorded, or until progression or relapse occurred, or if death from any cause occurred (in order of appearance). Patients who did not achieve CR or PR after first-line therapy were considered to have an EFS time of 0 days.

Response rates

Response to first-line chemotherapy was registered as recorded in the patient files. In RCTs, stringent rules are applied for determining response. However, valid comparisons with SLP response rates could not be made, as in SLP, response is often determined rather loosely and subjectively. This disadvantage should also be kept in mind when considering EFS. For this reason, both response and EFS were not used as main outcome parameters in this retrospective analysis.

Statistical analysis

The statistical analysis was performed using SPSS for Windows, version 11.0.1. All statistical tests were two-sided, with a significance level of $\alpha = 0.05$. Patient characteristics and treatment data were compared by Pearson's $\chi 2$ test in the case of discrete variables (or Fisher's Exact test, if appropriate), or -in the case of continuous variables- by the independent samples T-test (or Wilcoxon's rank sum test, if appropriate). All cost data are presented as mean values. As these data did not follow normal distributions, they were basically compared by Wilcoxon's rank sum test. Total costs were additionally compared by the non-parametric bootstrap test, as recommended, due to its independency with regard to the sample size distribution[15]. Univariate and multivariate regression analyses were performed on the natural logarithm of the original cost values, because of the normality assumption of these tests. OS was estimated by the Kaplan-Meier method[16]. The log-rank test was used for comparison of the survival curves[17].

Results

Patient characteristics

Characteristics of the 374 included patients are shown in Table 1.

Table 1. Patient characteristics.

	Younger patients (≤60 years)			Elderly patients (>60 years)		
	SLP	RCT	P	SLP	RCT	P
Total number of patients	105	80		81	108	
Age						
- mean (median; range)	47 (49; 16-60)	45 (47; 16-60)	0.169	71 (70; 61-84)	72 (72; 61-90)	0.081
Gender						
- male	58 (55.2%)	40 (50.0%)	0.552	46 (56.8%)	53 (49.1%)	0.307
- female	47 (44.8%)	40 (50.0%)		35 (43.2%)	55 (50.9%)	
Malignancy grade (WF)						
- Intermediate	89 (84.8%)	63 (78.8%)	0.126	62 (76.5%)	102 (94.4%)	0.001
- High	13 (12.4%)	9 (11.3%)		15 (18.5%)	5 (4.6%)	
- Unknown	3 (2.9%)	8 (10.0%)		4 (4.9%)	1 (0.9%)	
Extranodal involvement						
- Present	40 (38.1%)	49 (61.3%)	0.002	44 (54.3%)	60 (55.6%)	0.884
Spleen involvement						
- Present	15 (14.3%)	8 (10.0%)	0.501	10 (12.3%)	16 (14.8%)	0.675
Bone marrow involvement						
- Present	23 (22.1%)	23 (28.8%)	0.309	28 (34.6%)	36 (33.3%)	0.878
B-symptoms†						
- Present	31 (29.5%)	33 (41.3%)	0.119	25 (31.3%)	38 (35.2%)	0.640
IPI Ann Arbor stage						
- II	43 (41.0%)	15 (18.8%)	0.001	26 (32.1%)	31 (28.7%)	0.634
- III/IV	62 (59.0%)	65 (81.3%)		55 (67.9%)	77 (71.3%)	
IPI Serum LDH						
- ≤ 1x normal	66 (64.1%)	46 (57.5%)	0.445	42 (52.5%)	49 (45.4%)	0.377
- > 1x normal	37 (35.9%)	34 (42.5%)		38 (47.5%)	59 (54.6%)	
IPI Performance status						
- Ambulatory	101 (96.2%)	76 (96.2%)	1.000	71 (87.7%)	86 (79.6%)	0.172
- Not ambulatory	4 (3.8%)	3 (3.8%)		10 (12.3%)	22 (20.4%)	
IPI Number of extranodal sites						
- ≤1 site	96 (91.4%)	54 (67.5%)	0.000	67 (83.8%)	80 (74.1%)	0.153
- >1 site	9 (8.6%)	26 (32.5%)		13 (16.3%)	28 (25.9%)	
IPI Standard score*						
- Low (0-1)	73 (70.9%)	37 (46.8%)	0.001	14 (17.7%)	16 (14.8%)	0.209
- Low-intermediate (2)	23 (22.3%)	36 (45.6%)		31 (39.2%)	36 (33.3%)	
- High-intermediate (3)	7 (6.8%)	5 (6.3%)		23 (29.1%)	27 (25.0%)	
- High (4-5)	-	1 (1.3%)		11 (13.9%)	29 (26.9%)	
IPI Age adjusted score*						
- Low (0)	30 (29.1%)	1 (1.3%)	0.002	14 (17.5%)	16 (14.8%)	0.195
- Low-intermediate (1)	45 (43.7%)	56 (70.9%)		35 (43.8%)	42 (38.9%)	
- High-intermediate (2)	28 (27.2%)	21 (26.6%)		27 (33.8%)	34 (31.5%)	
- High (3)	-	1 (1.3%)		4 (5.0%)	16 (14.8%)	

WF: Working Formulation, IPI: International Prognostic Index for Aggressive non-Hodgkin's lymphomas, LDH: lactate dehydrogenase.
† B-symptoms: night sweats, fever (>38.3°C), or unexplained weight loss with >10% of the original body weight.
* IPI scores: these are based on age (≤ 60 vs. >60), stage (I/II vs. III/IV), serum LDH (≤1x normal vs. >1x normal), performance status (ambulatory vs. not ambulatory), and number of extranodal sites (≤1 vs >1). One point is calculated for each unfavourable variable. In the age adjusted score, age and number of extranodal sites are left out of consideration.

Compared to the SLP-YNG group, more patients in the RCT-YNG group had stage III/IV disease or >1 extranodal sites affected by NHL, which resulted in more RCT-YNG patients with unfavourable IPI[5] (International Prognostic Index for Aggressive NHL) scores. In the elderly patients, more patients in the RCT-ELD group had intermediate grade malignancy compared to the SLP-ELD group. All other variables showed comparable distributions.

Table 2 shows data on the 105+81 SLP patients who were not included in the considered RCTs: 15/105 (14% of younger patients) and 29/81 (36% of elderly patients) were not eligible for those trials due to exclusion criteria. The reasons for non-inclusion were unknown for 33 and 21 patients, respectively (this could not be determined retrospectively for these patients; it may for example be possible that the patient refused, that RCT participation was not offered, or that it was simply overlooked). However, they did not have severe co-morbidity, as 'co-morbidity' was one of the items that could be mapped reliably in this retrospective study. Therefore, 90/105 (86%) and 52/81 (64%) patients, respectively, did certainly not suffer from severe co-morbidity that might have prevented them from being included in an RCT. In principle, on biological grounds only, all of these patients would have been eligible to receive treatment according to the considered RCT protocols, except for 3+2 patients in whom histology was not conclusive ('aggressive NHL not otherwise specified'), and 5+1 patients under the age of 65 who could not be included in the HOVON NHL-26 trial due to their combinations of serum LDH and Ann-Arbor stage (see Table 2).

Table 2. Reasons why patients in the SLP groups were not included in one of the two considered RCTs.

Reason	Specification	Younger patients (≤60 years)	Elderly patients (>60 years)
Exclusion criterion for RCT present	Other or previous malignancy	6	11
	~ with inadequate renal and liver function	1	-
	~ with severe COPD	1	1
	~ with severe metabolic disease	1	-
	~ with severe heart failure	-	1
	Inadequate renal function	2	2
	Severe COPD	-	5
	Severe metabolic disease	-	1
	Severe heart failure	-	7
	~ with severe COPD	-	1
	HIV positivity	4	-
No active hospital participation policy		15	6
Uncertain histology		3	2
Informed consent not possible	due to severe psychological disorder	2	-
Not eligible for HOVON NHL-26 trial	due to serum LDH value*	5	1
Uncertainty about disease stage		2	1
Patient refusal		12	5
Practical obstacles	patient lives abroad	1	1
RCT not open for inclusion yet		17	15
Unknown (but no severe co-morbidity)		33	21
Total		105	81

* Patients were only included in the HOVON NHL-26 trial in the case of the following combinations: stage II + LDH ≥1.5x normal, stage III/IV + LDH <1.5x normal. COPD: chronic obstructive pulmonary disease.

Treatment characteristics

Table 3 presents treatment characteristics. Both in younger patients and in elderly patients, the mean number of chemotherapy cycles showed no difference between RCT and SLP and the majority of patients received 6 or 8 cycles. No significant differences were observed in the number of patients in whom dose reduction was applied, although this percentage appeared to be somewhat higher in the SLP-ELD group compared to the RCT-ELD group.

Table 3. Characteristics of the first-line treatment.

	Younger patients (≤60 years)		Elderly patients (>60 years)	
	SLP	RCT	SLP	RCT
Therapy modality:				
- Chemotherapy	84 (80.0%)	71 (88.8%)	67 (82.7%)	92 (85.2%)
- Chemotherapy followed by radiotherapy	21 (20.0%)	9 (11.3%)	14 (17.3%)	16 (14.8%)
Number of cycles:				
- Mean (median)	6.84 (7.00)	6.79 (6.00)	6.30 (6.00)	6.17 (6.00)
- 1	-	-	1 (1.2%)	1 (0.9%)
- 2	1 (1.0%)	-	-	6 (5.6%)
- 3	2 (1.9%)	1 (1.3%)	5 (6.2%)	8 (7.4%)
- 4	2 (1.9%)	2 (2.5%)	4 (4.9%)	6 (5.6%)
- 5	5 (4.8%)	5 (6.3%)	3 (3.7%)	6 (5.6%)
- 6	41 (39.0%)	34 (42.5%)	40 (49.4%)	36 (33.3%)
- 7	2 (1.9%)	1 (1.3%)	1 (1.2%)	1 (0.9%)
- 8	51 (48.6%)	37 (46.3%)	27 (33.3%)	44 (40.7%)
- 9	1 (1.0%)	-	-	-
Planned cycle interval:				
- 14 days	-	39 (48.8%)	-	2 (1.9%)
- 21 days	105 (100.0%)	41 (51.3%)	81 (100.0%)	106 (98.1%)
Doses of cytostatics (mean; median):				
- Cyclophosphamide iv	1231 (1350)	1411 (1587.5)	1134 (1300)	1301 (1307.5)
- Adriamycin iv	81 (90)	97 (107.5)	75 (87)	87 (90)
- Vincristine iv	2 (2)	2 (2)	2 (2)	2 (2)
- Prednisone orally (x5 days)	86 (100)	81 (100)	82 (100)	95 (100)
Dose reduction:				
- Applied	17 (16.2%)	11 (13.8%)	32 (39.5%)	34 (31.5%)
- Not applied	79 (75.2%)	62 (77.5%)	46 (56.8%)	72 (66.7%)
- Unknown	9 (8.6%)	7 (8.8%)	3 (3.7%)	2 (1.9%)
Haematopoietic growth factor support:				
- Applied	7 (6.7%)	41 (51.3%)	15 (18.5%)	52 (48.1%)
- Not applied	90 (85.7%)	39 (48.8%)	63 (77.8%)	56 (51.9%)
- Unknown	8 (7.6%)	-	3 (3.7%)	-
In case of haematopoietic growth factor support:				
- Applied at number of cycles (mean; median)	3.00 (3.00)	5.54 (6.00)	4.47 (5.00)	5.54 (6.00)
In case of radiotherapy:				
- Cumulative dose in Gy (mean; median)	35 (30)	39 (40)	37 (40)	33 (33)
- Number of fractions (mean; median)	18 (15)	19 (20)	18 (19)	14 (16)

Response

Of the younger patients, 74 (70.5%, SLP-YNG) and 49 (61.3%, RCT-YNG) reached CR following first-line treatment. PR was attained by 18 (17.1%, SLP-YNG), and 18 (22.5%, RCT-YNG) patients, 4 (3.8%, SLP-YNG) and 0 (0.0%, RCT-YNG) had stable disease, 4 (3.8%, SLP-YNG) and 7 (8.8%,

RCT-YNG) experienced progression during treatment, 0 (0.0%, SLP-YNG) and 1 (1.3%, RCT-YNG) died during treatment, and of 4 (4.8%, SLP-YNG) and 5 (6.3%, RCT-YNG) patients the treatment effect was unknown. In the elderly patients, treatment effects were as follows: 50 (61.7%, SLP-ELD) and 59 (54.6%, RCT-ELD) patients reached CR, 16 (19.8%, SLP-ELD) and 24 (22.2%, RCT-ELD) attained PR, 2 (2.5%, SLP-ELD) and 1 (0.9%, RCT-ELD) had stable disease, 10 (12.3%, SLP-ELD) and 10 (9.3%, RCT-ELD) experienced progression during treatment, 0 (0.0%, SLP-ELD) and 13 (12.0%, RCT-ELD) died during treatment, and of 3 (3.7%, SLP-ELD) and 1 (0.9%, RCT-ELD) patients treatment outcome was unknown.

Table 4. Mean (median) resource use and costs (Euros) of the first-line treatment.

	Younger patients (≤60 years)			Elderly patients (>60 years)		
	SLP	RCT	P†	SLP	RCT	P†
Resource use indicators:						
Hospital days for:						
- Therapy	2.57 (0.00)	3.44 (0.00)	0.498	4.40 (0.00)	8.73 (3.00)	0.018
- Fever	1.06 (0.00)	1.46 (0.00)	0.170	1.21 (0.00)	2.77 (0.00)	0.708
- General malaise	0.31 (0.00)	0.00 (0.00)	0.128	0.85 (0.00)	0.35 (0.00)	0.432
- Complications*	1.33 (0.00)	1.23 (0.00)	0.084	2.23 (0.00)	2.91 (0.00)	0.812
- Diagnostics	0.48 (0.00)	0.13 (0.00)	0.074	0.21 (0.00)	0.00 (0.00)	0.102
- Blood transfusions	0.00 (0.00)	0.00 (0.00)	1.000	0.19 (0.00)	0.02 (0.00)	0.087
- Other	0.93 (0.00)	1.58 (0.00)	0.917	1.22 (0.00)	0.61 (0.00)	0.144
- Total	6.69 (0.00)	7.83 (2.00)	0.309	10.31 (6.00)	15.39 (8.00)	0.069
Day care visits for:						
- Chemotherapy	6.51 (6.00)	6.09 (6.00)	0.692	5.21 (6.00)	4.98 (6.00)	0.758
- Other	0.27 (0.00)	0.46 (0.00)	0.244	0.46 (0.00)	0.53 (0.00)	0.199
Haematology outpatient visits	3.82 (3.00)	3.81 (3.00)	0.953	3.65 (3.00)	4.29 (3.00)	0.491
Costs:						
Hospital days	2127 (0)	2498 (636)	0.307	3278 (1908)	4894 (2544)	0.069
Haematology outpatient visits	231 (182)	231 (182)	0.953	221 (182)	259 (182)	0.491
Other outpatient visits	66 (0)	49 (0)	0.046	53 (0)	64 (0)	0.679
Day care treatments	962 (851)	929 (993)	0.945	804 (851)	782 (851)	0.490
Radiotherapy	671 (0)	411 (0)	0.157	583 (0)	407 (0)	0.570
Pathology diagnostics	107 (0)	98 (0)	0.182	62 (0)	119 (0)	0.068
Laboratory diagnostics	291 (181)	491 (318)	0.001	341 (277)	482 (407)	0.001
Microbiology diagnostics	46 (0)	87 (0)	0.010	48 (0)	87 (0)	0.192
Radiology diagnostics	629 (583)	870 (709)	0.016	593 (441)	969 (978)	0.000
Nuclear diagnostics	145 (0)	210 (0)	0.892	70 (0)	252 (213)	0.000
Other diagnostics	47 (0)	83 (0)	0.012	36 (0)	111 (20)	0.000
Blood components	172 (0)	452 (0)	0.048	198 (0)	480 (0)	0.001
Cytostatics	2621 (2633)	2777 (3015)	0.004	2186 (2303)	2296 (2429)	0.424
G-CSF	246 (0)	2970 (2093)	0.000	915 (0)	2825 (0)	0.000
Antibiotics	290 (0)	179 (0)	0.057	208 (0)	591 (106)	0.000
Other drugs	137 (2)	200 (27)	0.251	307 (45)	604 (430)	0.000
Total costs:						
- Excluding G-CSF‡	**8542 (6519)**	**9561 (7071)**	**0.204**	**8988 (7938)**	**12397 (10207)**	**0.000**
- 95% CI	7381-9703	8054-11068		7667-10308	10959-13835	
- Including G-CSF	8796 (6664)	12531 (11183)	0.000	9974 (7953)	15222 (13443)	0.000
- 95% CI	7559-10033	10732-14329		8427-11522	13600-16844	

* Complications could be related to NHL or to chemotherapy.
† As obtained by Wilcoxon's rank sum test.
‡ Main outcome measure.

Cost analysis: base case results

Base case results of the cost analysis are shown in Table 4. In the younger patients, no difference was shown on the main outcome measure (total costs excluding G-CSF), neither by Wilcoxon's rank sum test, nor by the bootstrap test, although some cost items were higher in the RCT group. Particularly costs of diagnostic tests were higher, which is probably due to tests required by protocol. Also, costs of blood components were higher in the RCT group, which might have been caused by a higher monitoring frequency in RCTs (laboratory diagnostics at each cycle), which increases the chance of applying supportive therapy on the basis of divergent values.

In the elderly patients, a significant difference occurred in the main outcome measure (also by the bootstrap test). The total number of hospital days for therapy was higher in the RCT-ELD group. The cost difference was caused by higher costs of diagnostic tests, blood components, antibiotics, and 'other drugs', for which we assume the same reasoning as stated above to be true. Analysing costs without patients who died during treatment did not affect any of these conclusions.

Table 5. Ordinary least squares regression analysis of the logarithm of the mean costs of first-line treatment (excl. G-CSF).

Independent variables†	Younger patients (≤60 years)		Elderly patients (>60 years)	
	b (se)	P-value	b (se)	P-value
Treatment group (0 = SLP, 1 = RCT)	0.048 (0.096)	0.618	0.291 (0.095)	0.003
IPI LDH category*	0.185 (0.090)	0.043	0.033 (0.096)	0.728
IPI Performance status category*	0.144 (0.230)	0.532	-0.014 (0.133)	0.916
IPI Stage category*	0.103 (0.103)	0.317	0.049 (0.108)	0.652
IPI Extranodal sites category*	0.177 (0.123)	0.151	0.166 (0.125)	0.186
Gender (0 = male, 1 = female)	-0.122 (0.090)	0.180	0.216 (0.095)	0.024
Age (continuous)	0.003 (0.004)	0.393	0.015 (0.008)	0.055
Intercept	8.621 (0.208)	0.000	7.677 (0.553)	0.000
Adjusted R^2	0.031		0.099	
F-value	1.837	0.083	3.926	0.001

† dependent variable: log(total costs first-line treatment excluding G-CSF).
* values of the IPI variables are 0 (favourable) and 1 (unfavourable).

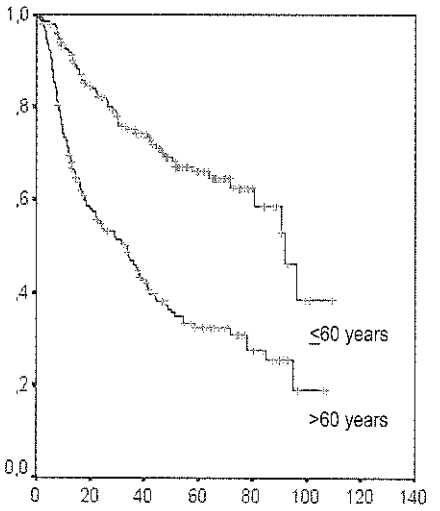
Cost analysis: base case regression analysis

Logarithmic transformations of Table 4's costs were used for the regression analysis. Three regression models were consequently generated: model 1 containing the 4 remaining prognostic factors of the IPI, model 1 to which age and gender were added (model 2), and model 2 to which 6 interaction terms (of the 4 IPI factors, age, and gender with the treatment group) were added (model 3). Model 2 turned out to have the best performance (according to F-value), and therefore Table 5 presents the results of this model. Table 5 confirms the results found in Table 4: for the younger patients, RCT inclusion did not influence the total costs. The only significant predictor for higher costs in younger patients was a serum LDH value higher than 1 times normal. In the elderly patients, RCT inclusion was a significant predictor of higher treatment costs. Back-transforming the regression

Discussion

We investigated if cost-efficacy of CHOP first-line chemotherapy for patients with aggressive NHL obtained in randomised clinical trials (RCTs) may be representative of cost-effectiveness obtained in standard local practice (SLP). The base case analysis showed that costs in younger patients were comparable within RCT and SLP, but suggested costs of first-line treatment in elderly patients to be higher in RCT. Matched pairs analyses (MPA) were performed to investigate the costs more thoroughly. The MPA basically confirmed the results. For the elderly patients, the final MPAs showed that the costs of RCT were only 11-13% higher than SLP costs. All in all, it seems reasonable to assume that including younger aggressive NHL patients in an RCT does not lead to cost increases, provided that treatments are comparable. Including elderly aggressive NHL patients in an RCT appears to cause some cost increase, but the exact increase seems to be modest. Survival analyses showed no difference if matched for clinical variables. The results of the cost and survival analyses lead us to the conclusion that in aggressive NHL, cost-efficacy as calculated within RCTs is quite representative of cost-effectiveness as obtained in daily clinical practice.

Figure 1. Overall survival from the start of treatment onwards (months).



In the past 25 years, despite many attempts, many newer chemotherapy schemes did not show superiority over the ancient standard CHOP regimen. Only the last few years, results on the treatment of NHL have emerged from stagnation[18]. Short-term perspectives look promising, which is particularly attributable to the introduction of the monoclonal antibody rituximab. The results of our analysis should therefore definitely not be interpreted as a proof of uselessness of RCTs. The design of RCTs is addressed to a high internal validity and not primarily to a high external validity. We only considered whether RCT results in aggressive NHL might nevertheless also be generalisable to daily clinical practice. In our belief, the positive finding regarding this question will only favour the usefullness of RCT results in aggressive NHL, beyond the ability of RCTs to appropriately verify or reject their main hypotheses.

Results of the elderly patients RCT used in this analysis (the HOVON NHL-25 trial) have been published in the meantime and no difference was shown in response and survival between both trial arms[8]. We therefore assumed this group as a whole to serve as a proper comparator to our SLP-ELD group. However, it might be that limitations exist on the ability of the HOVON NHL-25 trial itself to be representative of the 'average' elderly NHL patients RCT. A literature review on results obtained with

CHOP as the control arm in prospective randomised phase III clinical trials during the past 25 years showed that this trial had the lowest 2-year overall survival rate of 19 trials included in the analysis[3]. Moreover, in our random selection of 100 out of the 389 patients of this trial, 13% died during treatment, which is relatively high compared to the 5% of patients included in the entire study[8]. Given these considerations, it might be possible that we would have observed superiority of RCT survival over SLP survival in elderly patients when we had used another trial as the comparator to our SLP-ELD group. In this case, our results would have been perfectly comparable to a study in patients with Hodgkin's lymphoma, in which similar survival rates amongst RCT and SLP were observed in the case of age <45 years, but which showed a better survival of RCT over SLP in the case of age >65 years[19].
It has to be kept in mind that our conclusions are based on groups of patients who all underwent treatment, and that these treatments were intended to be curative. In practice, the condition of some patients with NHL only allows for palliative treatment or even no treatment at all. In a recent Dutch analysis, 10 out of 79 patients did not receive treatment because of their general condition[20]. The inclusion of this kind of patients in our SLP groups would of course have led to worse survival curves of these patients (and probably also to lower costs), and therefore to other conclusions.
All diagnostic cost items showed higher values in the RCT groups, but special attention should be paid to the costs of radiological imaging, which were 1.3-1.6 times higher in the case of RCT treatment. The recommendations in the protocols of both RCTs used in this analysis with regard to radiological imaging are not very different from standard recommendations (evaluation by imaging at mid-cycle and after treatment completion). Therefore, it should be concluded that in SLP, radiological imaging is not always performed according to 'best clinical practice recommendations'. The finding that more diagnostic tests were performed in the protocolled trial settings is an important one, because they were performed at 'clinical decision making moments', i.e. whether or not to continue the ongoing treatment or to switch to alternative therapy. By avoiding unnecessary and ineffective treatment in non-responding patients, this might justify the somewhat higher costs in elderly patients. It is sometimes suggested that in SLP diagnostic tests might be left undone if they do not alter treatment decisions, but in our opinion this is a misconception. If for example a bone-marrow biopsy for staging is not performed because the patient is already known to have stage IV NHL, one is not able to adequately assess the effect of the chemotherapy. The ignorance about a bone marrow localisation might lead to the erroneous conclusion that the patient has reached a complete remission, with the possibly fatal implication of not administering a second-line treatment or consolidation radiotherapy.
Furthermore, it might be possible that the somewhat higher costs in elderly patients could be prevented. Next to higher diagnostic costs, costs of hospitalisation contributed to the slightly higher costs in elderly RCT patients. The main type of hospital days that occurred more frequently was 'hospitalisation for therapy' (Table 4). The number of hospital days for complications was approximately the same amongst the SLP and RCT groups. This implies that the costs of elderly RCT patients can probably be reduced somewhat, because therapy might also be administered on an outpatient basis.

Although our main conclusion of comparability between RCT and SLP seems to conflict with general beliefs on this topic, earlier studies in other diseases focusing on generalisability of RCT results came to similar conclusions[21-31]. A recent review on outcomes in cancer patients treated within and outside clinical trials confirmed this result[32]. However, this kind of conclusions might not be valid for cases where a major part of the patient group is not eligible for trial inclusion, or in the case non-eligible patients suffer from characteristics that prevent them from being included in an RCT[33, 34]. Furthermore, generalisation will be hampered in diseases where more than one standard treatment exists, or in which no consensus about first-choice treatment has been reached. Generalisation from an RCT will also be more difficult in the case of treatments of which the result is highly dependent on patient compliance[35]. In general, generalisation should only be done after thorough assessment of the RCTs selection criteria[36, 37]. In this respect, generalisation is unfortunately hindered by many publications, as they fail to present detailed specifications of patients and treatments[27, 38].

Our finding that 14% of the younger SLP group and 36% of the elderly SLP group were not eligible for RCT inclusion seems to be supported by an earlier study in NHL, which demonstrated that the majority of younger NHL patients did not suffer from any co-morbidity, whereas many elderly NHL patients did[39]. Our conclusion that in SLP, some diagnostic tests are plausibly not always performed according to 'best clinical practice recommendations' is also supported by earlier studies in NHL[6, 40]. Comparable treatment results in aggressive NHL by the administration of comparable best available treatments to both SLP and RCT patients were also observed in a small recent Dutch study[20].

A limitation for the future representativeness of this study is the use of the Working Formulation[10] as lymphoma classification system. Due to the ever increasing insight that NHL consists of many subcategories with different prognoses, the 'Revised European-American classification of lymphoid neoplasms' (REAL), and its refined version published by the World Health Organization have now largely replaced this classification system[41, 42]. However, in the years considered by this study (1993-2001), the Working Formulation was the most widely used classification system and therefore the only possible histology selection system for this retrospective analysis.

In conclusion, in first-line treatment for aggressive NHL, we indicated cost-efficacy obtained in RCTs to be quite representative of cost-effectiveness obtained in daily clinical practice. When generalising costs and effects from RCTs to SLP, particular attention should be paid to comparability of the patient groups before any conclusions are drawn.

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Chapter 9. Cost determinants in aggressive non-Hodgkin's lymphoma

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Abstract

Context. For aggressive NHL, new pharmaceuticals appear on the market. Reimbursement decisions may be taken more adequately when subgroups can be identified in which pharmaceuticals may induce cost-effectiveness gains.

Objective. To analyse whether the International Prognostic Index (IPI) for Aggressive NHL and the presence of B-symptoms can identify subgroups of patients with (un)favorable cost profiles.

Design. Retrospective study, 1993-2001. Costs were calculated up to two years from the start of treatment.

Setting. Patient data from 4 university centres and 11 local hospitals were used.

Patients. Random sample of 374 patients with newly diagnosed stage II-IV aggressive NHL were collected by chart review and from administrative databases.

Interventions. First-line treatment with 6-8x CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, with or without granulocyte colony-stimulating factor (G-CSF).

Main outcome measures. Costs of first-line treatment and 2-year follow-up, both without costs of G-CSF, as some of the patients received these standard due to clinical trial participation.

Results. Mean costs of first-line treatment (excluding G-CSF) were €8983 (younger patients, ≤60 years) and €10936 (elderly patients, >60 years), 2-year follow-up (discounted) cost €12592 and €7924, respectively. The five individual IPI variables, the 2 IPI risk group variables (standard index and age-adjusted index) and B-symptoms all showed significant univariate associations with total first-line treatment costs. The same variables were associated with higher total 2-year costs, except for age, serum LDH, and standard risk group index. The lower predictability of total 2-year costs is due to the wide variations in number and types of second-line treatments applied.

Conclusion. The 5 individual IPI variables, the 2 IPI risk group variables, and the presence of B-symptoms can be used to distinguish groups of aggressive NHL patients according to cost profiles. Combined with its traditional use, the IPI can be used to predict cost-effectiveness in subgroups of aggressive NHL patients.

Introduction

Non-Hodgkin's Lymphoma (NHL) has the highest incidence rate of all haematological malignancies[1]. In the USA, the number of deaths attributable to NHL currently ranks in the top five of cancer related deaths, and NHL is amongst the small number of malignancies that have shown markedly increased incidence and mortality rates during the past decade[2, 3]. The group of NHL consists of a variety of different subtypes, of which aggressive NHL is the most prevalent, which is actually also a generic term for a category of lymphoid malignancies primarily consisting of diffuse large B-cell lymphomas (DLBCL). For aggressive NHL, the standard first-line treatment has been CHOP chemotherapy ever since 1976[4-6]. Only since a few years, research on the treatment of NHL has finally emerged from decades of stagnation[7]. This progress is particularly attributable to the introduction of rituximab, a monoclonal antibody targeted against the B-cell specific antigen CD20 present in approximately 80% of all DLBCL patients. However, in aggressive NHL, rituximab is applied in addition to the standard therapy, and is not a replacement of any current therapy. Such developments may have major financial consequences, as new pharmaceuticals are often relatively expensive. In some countries therefore, pharmaceutical companies will be obliged to provide information on the new drug's (expected) cost-effectiveness in addition to the required efficacy information, in order to have the drug considered for reimbursement[8].

Health care decision makers find themselves in a dilemma, given limited health care resources on the one hand, and high costs of potentially efficacious new pharmaceuticals on the other. Therefore, it might be beneficial if subgroups of patients can be identified at forehand, in whom new drugs are expected to lead to relatively large cost-effectiveness gains, given the costs and effects obtained in these patients with current therapies. Since its development in 1993, the International Prognostic Index (IPI) for aggressive NHL has been used worldwide to distinguish aggressive NHL patients according to their effect rates (i.e. survival)[9]. However, no such system exists for the identification of aggressive NHL patients with (un)favourable cost profiles, nor has it ever been tested if the IPI is capable of doing so, which is probably due to the fact that most cost analyses in NHL have only been based on relative small sample sizes. Therefore, in a group of 374 aggressive NHL patients, we analysed if associations between the (un)favourable IPI risk profiles with total treatment costs could be identified. In addition, the presence of B-symptoms (night sweats, fever, weight loss) was tested as a predictive variable, as we assumed patients with disease related symptoms to require more supportive care and as a result to generate higher costs.

Patients and Methods

Patients

This retrospective study was based on data of patients with newly diagnosed aggressive NHL (intermediate or high-grade malignancy according to the Working Formulation, groups D-H[10]), stage II-IV (disseminated disease) according to the Ann-Arbor classification[11], who underwent standard first-line CHOP chemotherapy between 1993 and 2001 (CHOP: cyclophosphamide iv 750 mg/m^2 day 1, adriamycin iv 50 mg/m^2 day 1, vincristine iv 1.4 mg/m^2 (max. 2 mg) day 1, prednisone orally 100 mg day 1-5, repeated at 21-days intervals). Two age groups were defined, based on the IPI: younger patients ($\leq$60 years) and elderly patients (>60 years)[9]. The aim was to include approximately 200 patients in both groups (number set by practical considerations). In the years covered by this analysis, two randomised controlled trials (RCTs) were performed in these patients: the HOVON (Dutch Working Group on Adult Haemato-Oncology) NHL-25 trial, comparing CHOP with CHOP + prophylactic administration of granulocyte colony-stimulating factor (G-CSF) in patients $\geq$65 years, in order to investigate whether G-CSF could reduce the severity and duration of leukopenia and infections, which often necessitates dose reduction[12]. Patients 15-65 years could be included in the HOVON NHL-26 trial, which compared 8x CHOP to 6x intensified (14 days cycle interval; higher cyclophosphamide and doxorubicin doses) CHOP+G-CSF, under the hypothesis that the exposure of tumour cells to several non-cross resistant drugs at the maximum tolerated dose and given as early as possible may circumvent the development of drug resistance[13]. Next to patients who received CHOP according to standard practice, patients from these RCTs were also included in our analysis. Patients were selected from consecutive lists by haematologists from 15 hospitals. Patients with lymphoblastic lymphomas were not included because of a different prognosis.

Cost analysis

Costs were calculated from the start of first-line treatment up to 2 years afterwards. Within this period, up to 4 phases per patient were distinguished. All patients underwent first-line treatment (TR1). Except if the patient died during or after first-line treatment, the patient moved to 'follow-up 1' (FU1), or –in case of insufficient response or resistance to TR1- immediately to second-line treatment (TR2). FU1 lasted until the date '2 years after start of first-line treatment' had been reached, or until death or disease progression. If no treatment was administered for progression, the patient moved to 'follow-up 2' (FU2). If treatment for progression was initiated, the patient moved to TR2. After TR2, the patient moved to FU2, except if the patient had died during or immediately after treatment. FU2 lasted until the date '2 years after start of first-line treatment' had been reached, or until death or a second disease progression. In the latter case, the patient was censored from that date onwards (third-line treatments were excluded from the analysis). The main outcome measure was 'total cost excluding G-CSF'. Costs including G-CSF were considered to be misleading, given the 2 RCTs in which half of the

patients received G-CSF by default. If not specifically mentioned, all costs considerations relate to costs without costs of G-CSF administered during first-line treatment.

The cost analysis was performed from the hospital perspective[14], and therefore based on all medical resource use generated within the hospital in the 2-year time frame, which data were collected from anonymous databases, generated by administrative departments of the hospitals. Drug use at home was also included, and estimated from notes in patient files. Resource use for co-morbidity was not recorded. For the valuation of the most important items within the resource use, separate unit costs were calculated (Euro, price level 2000) reflecting full hospital costs[15, 16]. To determine these unit costs, we applied the micro-costing method, which is based on a detailed inventory and measurement of resources consumed[17]. Unit costs as calculated on the basis of financial data from five of the participating hospitals were: inpatient hospital day €318 of which 57% personnel costs (P), 14% material costs (M), and 29% overhead costs (O); haematology outpatient visit €61 of which P80%, M4%, O16%; other outpatient visit €55 of which P80%, M4%, O16%; day care treatment €142 of which P44%, M18%, O38%; radiotherapy megavolt session (including raise for preparation costs) €191 of which P62%, M15%, O23%; lymph node biopsy under general anaesthesia €555, of which P46%, M31%, O23%; peripheral blood stem cell transplantation's (PBSCT) procedural costs (harvesting, freezing, and defrosting transplant) € 2231, of which P36%, M44%, O20%. For items with low costs or minor influence (due to low average numbers), Dutch charges were used as approximations, as they are assumed to appropriately reflect actual costs[15]. Costs of medication were based on Dutch wholesale prices[18]. Costs made in the second year were discounted at a recommended rate of 4%[19].

Survival analysis

On behalf of the survival analysis, patients were followed as long as possible. The overall survival (OS) time was calculated from the start of the first-line treatment onwards.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 11.0.1. In order to determine univariate associations between patient characteristics and costs, total costs were compared by the non-parametric bootstrap test. This test is recommended for health care economic evaluations, given the fact that cost distributions are almost always skewed and the independency of the bootstrap test with regard to the sample size distribution[20, 21]. Univariate and multivariate regression analyses were performed on the natural logarithm of the original cost values, because of the normality assumption of these tests. Step-down regression analyses were performed using a $P \leq 0.05$ probability of F to enter, and a $P \geq 0.10$ probability of F to remove. OS was estimated by the Kaplan-Meier method[22].

Results

Patient characteristics and survival

Characteristics of the 374 patients are shown in Table 1. Overall survival according to age and IPI risk groups is shown in Figure 1.

Table 1. Patient characteristics.

	Younger patients	Elderly patients	All
Total number of patients	185	189	374
Age			
- mean (median; range)	46 (48; 16-60)	72 (72; 60-90)	59 (61; 16-90)
Gender			
- male	98 (53.0%)	99 (52.4%)	197 (52.7%)
- female	87 (47.0%)	90 (47.6%)	177 (47.3%)
Malignancy grade (WF)			
- intermediate	152 (82.2%)	164 (86.8%)	316 (84.5%)
- high	22 (11.9%)	20 (10.6%)	42 (11.2%)
- unknown	11 (5.9%)	5 (2.6%)	16 (4.3%)
B-symptoms†			
- present	64 (34.6%)	63 (33.5%)	127 (34.0%)
IPI Ann Arbor stage			
- II	58 (31.4%)	57 (30.2%)	115 (30.7%)
- III/IV	127 (68.6%)	132 (69.8%)	259 (69.3%)
IPI Serum LDH			
- ≤ 1x normal	112 (61.2%)	91(48.4%)	203 (54.7%)
- > 1x normal	71 (38.8%)	97 (51.6%)	168 (45.3%)
IPI Performance status			
- ambulatory	177 (96.2%)	157 (83.1%)	334 (89.5%)
- not ambulatory	7 (3.8%)	32 (16.9%)	39 (10.5%)
IPI Number of extranodal sites			
- ≤ 1 site	150 (81.1%)	147 (78.2%)	297 (79.6%)
- > 1 site	35 (18.9%)	41 (21.8%)	76 (20.4%)
IPI Standard score*			
- low (0-1)	110 (60.4%)	30 (16.0%)	140 (37.9%)
- low-intermediate (2)	59 (32.4%)	67 (35.8%)	126 (34.1%)
- high-intermediate (3)	12 (6.6%)	50 (26.7%)	62 (16.8%)
- high (4-5)	1 (0.5%)	40 (21.4%)	41 (11.1%)
IPI Age adjusted score*			
- low (0)	31 (17.0%)	30 (16.0%)	61 (16.5%)
- low-intermediate (1)	101 (55.5%)	77 (41.0%)	178 (48.1%)
- high-intermediate (2)	49 (26.9%)	61 (32.4%)	110 (29.7%)
- high (3)	1 (0.5%)	20 (10.6%)	21 (5.7%)

WF: Working Formulation, IPI: International Prognostic Index for Aggressive non-Hodgkin's lymphomas, LDH: lactate dehydrogenase.
† B-symptoms: night sweats, fever (>38.3°C), or unexplained weight loss with >10% of the original body weight.
* IPI scores: these are based on age (≤ 60 vs. >60), stage (I/II vs. III/IV), serum LDH (≤1x normal vs. >1x normal), performance status (ambulatory vs. not ambulatory), and number of extranodal sites (≤1 vs >1). One point is calculated for each unfavorable variable. In the age adjusted score, age and number of extranodal sites are left out of consideration.

Treatment characteristics

Table 2 presents characteristics of the first-line treatment. On average, younger patients received 6.82 CHOP cycles, whereas the elderly patients received 6.22 cycles (P=0.001). The majority of the patients received ≥6 cycles, as recommended. The percentage of patients for whom dose reduction

was applied, was higher in elderly patients (34.4% vs. 15.1%, P=0.001). The drug of which the dose was most frequently reduced was vincristine, usually because of neuropathy.

Figure 1. Overall survival from the start of treatment onwards (months), distinguished to age (1a, left) and risk group of the International Prognostic Index for Aggressive NHL (1b, right).

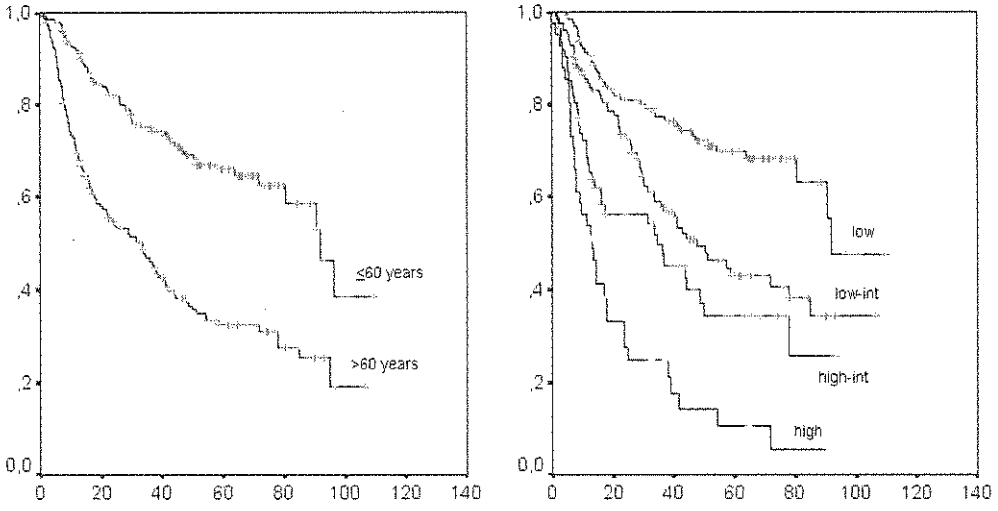


Table 2. Characteristics of the first-line CHOP treatment.

	Younger patients	Elderly patients
Therapy modality:		
- Chemotherapy	155 (83.8%)	159 (84.1%)
- Chemotherapy followed by radiotherapy	30 (16.2%)	30 (15.9%)
Number of cycles:		
- Mean (median)	6.82 (6.00)	6.22 (6.00)
- 1 to 5	18 (9.7%)	38 (20.3%)
- 6 to 9	167 (90.3%)	149 (79.7%)
Planned cycle interval:		
- 14 days	39 (21.1%)	2 (1.1%)
- 21 days	146 (78.9%)	187 (98.9%)
Dose reduction:		
- Applied	28 (15.1%)	65 (34.4%)
- Not applied	141 (76.2%)	118 (62.4%)
- Unknown	16 (8.6%)	6 (3.2%)
In case of dose reduction, total relative dose administered:		
- Cyclophosphamide iv	83.0%	82.7%
- Adriamycin iv	84.8%	81.5%
- Vincristine iv	50.9%	45.4%
- Prednisone orally (x5 days)	95.5%	88.5%
In case of radiotherapy:		
- Cumulative dose in Gy (mean; median)	36 (36)	35 (38)
- Number of fractions (mean; median)	18 (18)	16 (17.5)

Cost analysis

Table 3 presents resource use and costs of the first-line treatment (TR1) and the consequent follow-up (up to 2 years, undiscounted) according to an intention-to-treat principle, implying that the mean follow-up costs were calculated on the basis of the initial cohorts of 185 younger patients (Y) and 189 elderly patients (E). 'Follow-up total' in Table 3 is therefore the sum of 'Follow-up 1' (FU1), 'Second-line treatment' (TR2), and 'Follow-up 2' (FU2). The latter three phases were actually completed by 146 (Y) + 161 (E), 68 (Y) + 48 (E), and 46 (Y) + 28 (E) patients, respectively. Of the 185 (Y) and 189 (E) patients, the majority only passed through phases TR1>FU1 (109Y+118E) during the 2-year period. The remainder of the patients had the following 2-year courses: TR1>FU1>FU2 (2Y+6E), TR1>FU1>TR2 (15Y+19E), TR1>FU1>TR2>FU2 (20Y+18E), TR1 only (6Y+17E), TR1>TR2 (9Y+7E), TR1>TR2>FU2 (24Y+4E). Table 3 reflects that mean follow-up durations were 608 (Y) and 518 (E) days, respectively.

Table 3 shows that mean costs of TR1 without G-CSF were €8983 (Y) vs. €10936 (E). The difference was caused by hospitalisation costs, as elderly patients were hospitalised more often during TR1. Costs of FU1 were €3150 (Y) vs. €3901 (E) for average FU1 durations of 363 and 312 days, respectively.

Total 2-year costs (excluding costs of G-CSF administered during TR1) were €21788 (95%CI €19106-€24470) in younger patients and €18984 (95%CI €17038-€20931) in elderly patients. When costs of the second year are discounted, these costs amounted to €21575 (95%CI €18927-€24222), and €18860 (95%CI €16937-€20784), respectively.

When averaged over all patients initially treated, mean costs of second-line treatments appeared to be lower in elderly patients (Table 3). This is due to the fact that more younger patients (68) than elderly patients (48) underwent second-line treatments. Costs of patients who underwent second-line treatments are specified in Table 4 (notice that costs of 1 elderly patient who underwent high-dose chemotherapy followed by PBSCT were left out of consideration). This table shows that costs of chemotherapy as second-line treatment were comparable amongst younger and elderly patients. Costs of cytostatics were relatively high in elderly patients due to a large proportion of patients undergoing expensive schemes. In both groups, chemotherapy was followed by radiotherapy in 2 patients. No agreement on second-line chemotherapy existed: 12 different schemes were applied in younger patients, and 22 different schemes in elderly patients.

On the basis of patients who spent their entire FU1 in complete remission after first-line chemotherapy, and who reached the scheduled endpoint of the 2-year timeframe of this analysis (84Y+64E), mean monthly costs of 'regular' follow-up were calculated. These costs amounted to €171 (median €94, 95%CI €108-€234) in younger patients, and €174 (median €78, 95% CI €103-€245) in elderly patients. Main cost drivers were hospital days (Y33%, E44%), radiology diagnostics (Y27%, E14%), haematology outpatient visits (Y13%, E13%), and laboratory diagnostics (Y10%, E8%).

Table 3. Mean (median) resource use and costs of the first-line treatment and 2-year follow-up (undiscounted), according to intention-to-treat principle.

	First-line treatment		Follow-up 1		Second-line treatment		Follow-up 2		Follow-up total	
	Younger patients	Elderly patients	Younger patients	Elderly patients	Younger patients	Elderly patients	Younger patients	Elderly patients	Younger patients	Elderly patients
Resource use indicators:										
Hospital days for:										
- Therapy	2.95 (0.00)	6.87 (2.00)	0.15 (0.00)	0.79 (0.00)	9.60 (0.00)	1.56 (0.00)	0.39 (0.00)	0.17 (0.00)	10.14 (0.00)	2.52 (0.00)
- Fever	1.23 (0.00)	2.10 (0.00)	0.40 (0.00)	0.76 (0.00)	0.55 (0.00)	0.43 (0.00)	0.21 (0.00)	0.25 (0.00)	1.15 (0.00)	1.44 (0.00)
- General malaise	0.18 (0.00)	0.57 (0.00)	0.00 (0.00)	1.30 (0.00)	0.00 (0.00)	0.42 (0.00)	0.12 (0.00)	0.22 (0.00)	0.12 (0.00)	1.94 (0.00)
- Complications*	1.29 (0.00)	2.62 (0.00)	1.08 (0.00)	2.05 (0.00)	0.27 (0.00)	0.85 (0.00)	0.35 (0.00)	0.48 (0.00)	1.70 (0.00)	3.37 (0.00)
- Diagnostics	0.32 (0.00)	0.09 (0.00)	1.11 (0.00)	0.43 (0.00)	0.04 (0.00)	0.14 (0.00)	0.17 (0.00)	0.06 (0.00)	1.32 (0.00)	0.63 (0.00)
- Blood transfusions	0.00 (0.00)	0.09 (0.00)	0.00 (0.00)	0.00 (0.00)	0.02 (0.00)	0.03 (0.00)	0.01 (0.00)	0.08 (0.00)	0.03 (0.00)	0.11 (0.00)
- Other	1.21 (0.00)	0.87 (0.00)	0.80 (0.00)	1.86 (0.00)	0.24 (0.00)	0.06 (0.00)	0.05 (0.00)	0.08 (0.00)	1.10 (0.00)	2.01 (0.00)
- Total	7.18 (0.00)	13.21 (7.00)	3.54 (0.00)	7.19 (0.00)	10.71 (0.00)	3.49 (0.00)	1.30 (0.00)	1.35 (0.00)	15.55 (0.00)	12.03 (0.00)
Day care visits for:										
- Chemotherapy	6.33 (6.00)	5.08 (6.00)	0.00 (0.00)	0.00 (0.00)	0.77 (0.00)	0.74 (0.00)	0.00 (0.00)	0.00 (0.00)	0.77 (0.00)	0.74 (0.00)
- Other	0.35 (0.00)	0.50 (0.00)	0.23 (0.00)	0.17 (0.00)	0.43 (0.00)	0.14 (0.00)	0.16 (0.00)	0.07 (0.00)	0.82 (0.00)	0.39 (0.00)
Haematology outpatient visits	3.82 (3.00)	4.02 (3.00)	5.13 (5.00)	4.79 (5.00)	1.57 (0.00)	1.70 (0.00)	1.65 (0.00)	0.38 (0.00)	8.35 (7.00)	6.87 (6.00)
Phase duration	146 (158)	152 (149)	363 (489)	312 (294)	37 (0)	39 (0)	62 (0)	15 (0)	462 (559)	366 (471)
Costs:										
Hospital days	2288 (0)	4201 (2226)	1128 (0)	2287 (0)	3436 (0)	1109 (0)	416 (0)	433 (0)	4980 (0)	3829 (0)
Haematology outpatient visits	231 (182)	243 (182)	310 (303)	290 (303)	95 (0)	103 (0)	100 (0)	23 (0)	505 (424)	416 (363)
Other outpatient visits	58 (0)	59 (0)	77 (0)	77 (0)	27 (0)	18 (0)	16 (0)	4 (0)	120 (55)	99 (0)
Day care treatments	948 (993)	791 (851)	32 (0)	24 (0)	170 (0)	125 (0)	23 (0)	11 (0)	225 (0)	159 (0)
Radiotherapy	559 (0)	482 (0)	31 (0)	58 (0)	45 (0)	103 (0)	50 (0)	13 (0)	126 (0)	174 (0)
Pathology diagnostics	103 (0)	94 (0)	116 (0)	67 (0)	92 (0)	42 (0)	13 (0)	10 (0)	221 (0)	120 (0)
Laboratory diagnostics	377 (235)	421 (373)	250 (163)	218 (150)	253 (0)	97 (0)	50 (0)	35 (0)	553 (335)	350 (227)
Microbiology diagnostics	64 (0)	70 (0)	38 (0)	27 (0)	231 (0)	20 (0)	11 (0)	10 (0)	280 (0)	57 (0)
Radiology diagnostics	733 (620)	808 (772)	730 (568)	399 (129)	333 (0)	126 (0)	142 (0)	60 (0)	1204 (942)	585 (336)
Nuclear diagnostics	173 (0)	174 (0)	116 (0)	37 (0)	816 (0)	106 (0)	28 (0)	3 (0)	961 (0)	146 (0)
Other diagnostics	62 (0)	79 (0)	62 (0)	87 (0)	236 (0)	39 (0)	7 (0)	9 (0)	305 (0)	135 (0)
Blood components	293 (0)	359 (0)	117 (0)	70 (0)	0 (0)	82 (0)	142 (0)	35 (0)	259 (0)	187 (0)
PBSCT	0 (0)	0 (0)	0 (0)	0 (0)	350 (0)	12 (0)	0 (0)	0 (0)	350 (0)	12 (0)
Cytostatics	2687 (2865)	2249 (2310)	0 (0)	0 (0)	1424 (0)	1190 (0)	0 (0)	0 (0)	1424 (0)	1190 (0)
G-CSF	1477 (0)	2024 (0)	0 (0)	0 (0)	339 (0)	88 (0)	0 (0)	0 (0)	339 (0)	89 (0)
Antibiotics	242 (0)	426 (7)	35 (0)	99 (0)	246 (0)	93 (0)	86 (0)	23 (0)	367 (0)	215 (0)
Other drugs	164 (4)	477 (169)	107 (0)	162 (0)	124 (0)	130 (0)	102 (0)	18 (0)	333 (6)	309 (13)
Total costs:										
- Excluding G-CSF	**8983 (6664)**	**10936 (9097)**	**3150 (1551)**	**3901 (1216)**	**7877 (0)**	**3394 (0)**	**1186 (0)**	**687 (0)**	**12213 (3964)**	**7981 (3047)**
- 95% CI	8061-9953	9969-12026	2210-4090	2805-4996	5870-9884	2289-4499	642-1729	210-1164	10045-14807	6291-9504
- Including G-CSF	10484 (7933)	13021 (11327)	3150 (1551)	3901 (1216)	8216 (0)	3482 (0)	1186 (0)	687 (0)	12552 (3964)	8070 (3047)
- 95% CI	9401-11567	11827-14216	2210-4090	2805-4996	6147-10286	2341-4624	642-1729	210-1164	10337-15224	6358-9616

* Complications could be related to NHL or to chemotherapy. PBSCT = peripheral blood stem cell transplantation. G-CSF = granulocyte colony stimulating factor.

Table 4. Mean (median) resource use and costs of second-line treatments, according to per-protocol principle.

	Younger patients		Elderly patients	
	Chemotherapy	High-dose chemo-therapy + PBSCT	Chemotherapy	Radiotherapy
	(n=39)	(n=29)	(n=42)	(n=5)
Resource use indicators:				
Hospital days for:				
- Therapy	15.54 (14.00)	40.34 (37.00)	7.02 (0.00)	0.00 (0.00)
- Fever	1.92 (0.00)	0.90 (0.00)	1.95 (0.00)	0.00 (0.00)
- General malaise	0.00 (0.00)	0.00 (0.00)	1.19 (0.00)	5.80 (0.00)
- Complications*	1.03 (0.00)	0.34 (0.00)	3.40 (0.00)	3.40 (0.00)
- Diagnostics	0.03 (0.00)	0.21 (0.00)	0.62 (0.00)	0.00 (0.00)
- Blood transfusions	0.00 (0.00)	0.10 (0.00)	0.14 (0.00)	0.00 (0.00)
- Other	1.08 (0.00)	0.10 (0.00)	0.26 (0.00)	0.00 (0.00)
- Total	19.59 (18.00)	42.00 (37.00)	14.60 (7.00)	9.20 (0.00)
Day care visits for:				
- Chemotherapy	2.74 (0.00)	1.21 (0.00)	3.31 (1.00)	0.00 (0.00)
- Other	0.72 (0.00)	1.76 (1.00)	0.64 (0.00)	0.00 (0.00)
Haematology outpatient visits	3.72 (2.00)	5.00 (5.00)	7.31 (5.00)	2.80 (3.00)
Phase duration	76 (61)	136 (125)	161 (120.5)	99 (82)
Costs:				
Hospital days	6249 (5724)	13517 (12084)	4641 (2226)	2926 (0)
Haematology outpatient visits	225 (121)	303 (303)	442 (303)	169 (182)
Other outpatient visits	55 (0)	97 (55)	76 (0)	33 (0)
Day care treatments	491 (142)	421 (142)	561 (284)	0 (0)
Radiotherapy	171 (0)	59 (0)	68 (0)	3324 (3821)
Pathology diagnostics	239 (76)	263 (152)	162 (90)	247 (242)
Laboratory diagnostics	626 (536)	770 (568)	387 (305)	210 (163)
Microbiology diagnostics	381 (81)	959 (729)	90 (0)	5 (0)
Radiology diagnostics	771 (671)	1088 (914)	521 (285)	381 (357)
Nuclear diagnostics	1565 (213)	3103 (1134)	474 (0)	32 (0)
Other diagnostics	441 (0)	913 (688)	176 (20)	15 (0)
Blood components	0 (0)	0 (0)	358 (0)	75 (0)
PBSCT	0 (0)	2231 (0)	0 (0)	0 (0)
Cytostatics	3375 (2686)	4543 (4121)	5256 (2653)	0 (0)
G-CSF	583 (0)	1381 (1116)	398 (0)	0 (0)
Antibiotics	379 (82)	1062 (299)	418 (3)	20 (0)
Other drugs	201 (137)	522 (467)	545 (208)	319 (0)
Total costs:				
- Excluding G-CSF	**15170**	**29850**	**14175**	**7757**
	(12238)	**(24205)**	**(11933)**	**(5568)**
- 95% CI	11824-18515	23488-36211	10927-17422	2305-13209
- Including G-CSF	15752	31231	14573	7757
	(12407)	(26140)	(12030)	(5568)
- 95% CI	12304-19201	24931-37531	11189-17957	2305-13209

* Complications could be related to NHL or to chemotherapy. PBSCT = peripheral blood stem cell transplantation. G-CSF = granulocyte colony stimulating factor.

Univariate analysis of cost determinants

Table 5 shows the univariate association of treatment costs with individual patient characteristics. First, the association between the characteristics and the treatment costs, as calculated by the non-parametric bootstrap test, is presented. The mean costs within the (un)favourable categories and the mean cost difference (and 95% confidence intervals) are presented. With regard to first-line treatment costs, the presence of B-symptoms and all unfavourable categories of the IPI scoring system (IPI performance status very close to significant) were associated with higher costs. Higher total 2-year

costs were associated with the presence of B-symptoms, advanced stage, unfavourable performance status and >1 extranodal sites involved by NHL.

Second, univariate regression analyses were performed on the natural logarithm of the costs, which confirmed the results of the bootstrap tests: all characteristics showed significant univariate associations with first-line treatment costs, and all but age and serum LDH with total 2-year costs.

Table 5. Mean costs (excluding G-CSF) according to individual clinical characteristics, as calculated by the non-parametric bootstrap test, and univariate associations of these characteristics with the natural logarithm of the costs, as calculated by univariate regression analyses (URA).

	First-line treatment costs			Total 2-year costs (discounted)		
	Bootstrap test		URA	Bootstrap test		URA
	Mean	95%CI	P-value	Mean	95%CI	P-value
B-symptoms						
- absent	9316	8543-10196		17988	16387-19757	
- present	11272	10085-12513		24064	20874-27356	
- difference	1956†	509-3536	0.002	6077†	2511-9782	0.000
IPI Age						
- ≤60 years	8993	8068-9958		21299	18944-23959	
- >60 years	10968	9956-12013		18877	16990-20864	
- difference	1975†	483-3456	0.006	-2422	-5669-769	0.469
IPI Ann Arbor stage						
- II	8688	7807-9706		17198	14844-19802	
- III/IV	10534	9751-11348		21339	19422-23381	
- difference	1846†	619-3074	0.032	4141†	966-7404	0.018
IPI Serum LDH						
- ≤ 1x normal	9403	8476-10381		19926	17645-22316	
- > 1x normal	10711	9756-11774		20286	18145-22607	
- difference	1307‡	-128-2657	0.012	360	-2815-3516	0.444
IPI Performance status						
- ambulatory	9687	8984-10444		19643	17947-21327	
- not ambulatory	12650	10254-15472		24463	20365-29030	
- difference	2963†	502-5818	0.055	4820†	279-9556	0.025
IPI Number of extranodal sites						
- ≤ 1 site	9366	8650-10097		19321	17590-21094	
- > 1 site	12367	10615-14229		23319	19609-26998	
- difference	3001†	1039-4818	0.002	3998‡	-45-7943	0.022

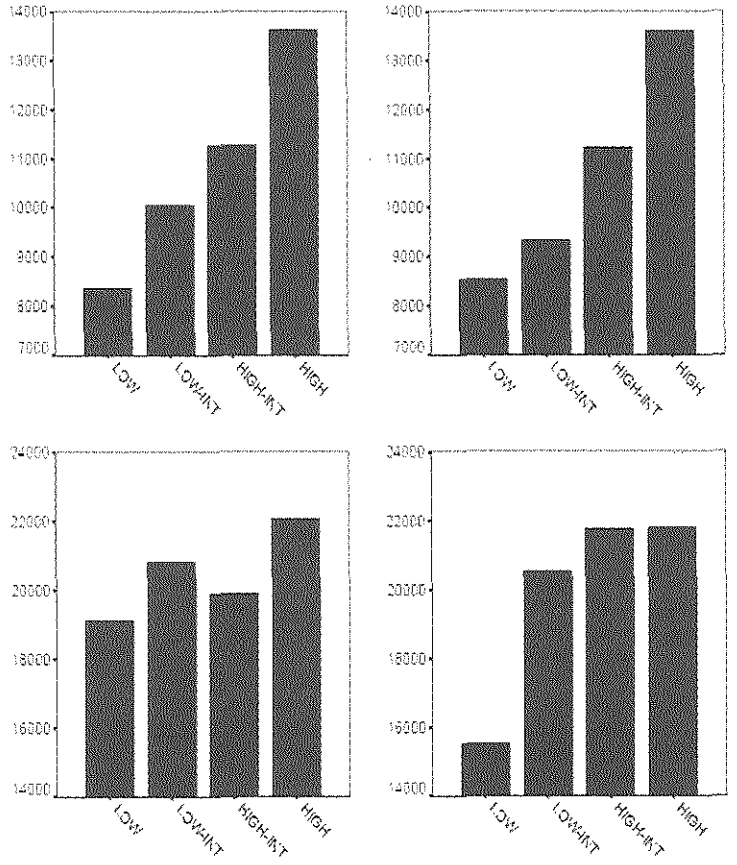
G-CSF: granulocyte colony-stimulating factor, CI: confidence interval, IPI: International Prognostic Index for Aggressive NHL, LDH: lactate dehydrogenase.
† Significant difference according to bootstrap test.
‡ Very close to significant difference according to bootstrap test.

The finding that not all variables of the IPI are predictive for total 2-year costs is most plausibly caused by the fact that more younger than elderly patients underwent second-line treatments and that second-line costs varied considerably by modality (Table 4).

Figure 2 shows the total costs according to IPI risk groups. Figures 2a-2b demonstrate that both the standard IPI and the age-adjusted IPI are very well able to distinguish different first-line treatment costs according to risk group. This finding is confirmed by univariate regression analysis on the natural logarithm of the total first-line costs, as the associations with the standard IPI (intercept b=8.847, se=0.047, P=0.000; IPI risk group b=0.094, se=0.020, P=0.000) and the age-adjusted IPI are

significant (intercept b=8.828, se=0.061, P=0.000; IPI risk group b=0.147, se=0.041, P=0.000). Figures 2c-2d distinguish total 2-year costs to IPI risk group. Univariate regression analyses showed that the IPI standard score is not predictive of total 2-year costs (intercept b=9.565, se=0.057, P=0.000; IPI risk group b=0.042, se=0.024, P=0.079), but the IPI age-adjusted score showed a significant association (intercept b=9.475, se=0.072, P=0.000; IPI risk group b=0.131, se=0.049, P=0.008), although the differences are less obvious as compared to first-line treatment costs. Again, we assume this to be due to differences in numbers and types of second-line treatments applied.

Figure 2. Total costs according to the risk groups of the International Prognostic Index (IPI) for Aggressive NHL: first-line treatment costs according to IPI standard index (2a, upper left), first-line treatment costs according to IPI age-adjusted index (2b, upper right), total 2-year costs according to IPI standard index (2c, lower left), total 2-year costs according tot IPI age-adjusted index (2d, lower right). All cost figures exclude costs of G-CSF administered during first-line treatment.



The positive linear relationship between IPI risk group and total costs is primarily caused by a larger number of hospital days in the more unfavourable risk groups. Whereas the relative contributions of all other cost items remain constant or even decrease, the relative contribution of hospitalisation costs in the total first-line treatment costs (Figure 2a) rises from 22% (low risk), 34% (low-intermediate), 38% (high-intermediate), to 45% (high risk). For figure 2b, these percentages are 22%, 30%, 38%, and 47%, respectively.

Multivariate analysis of cost determinants

Table 6 shows the results of the ordinary least squares regression analysis on the natural logarithm of the total costs. When combined into one model, three out of five IPI variables remain significant predictors of total costs (age, serum LDH, and extranodal sites). When the variable B-symptoms is added (not shown), this becomes the most significant predictor, whereas the variable serum LDH loses its significancy. Again, total 2-year costs turned out to be less predictable, as performance status was the only significant variable in this multivariate model (Table 6). When B-symptoms is added (not shown), this is the only significant variable within the model.

If one prefers a multivariate model over a univariate model, stepwise regression analyses on the natural logarithm of the total costs showed that a model consisting of an intercept (b=8.808, se=0.053, P=0.000), B-symptoms (b=0.210, se=0.068, P=0.002), IPI extranodal sites (b=0.228, se=0.080, P=0.005), and IPI age (b=0.165, se=0.065, P=0.011) performed best with regard to first-line treatment costs. With regard to total 2-year costs, such a model would consist of an intercept (b=9.501, se=0.051, P=0.000), B-symptoms (b=0.275, se=0.081, P=0.001), and IPI extranodal sites (b=0.203, se=0.095, P=0.033).

Table 6. Ordinary least squares regression analysis of the logarithm of the total costs (excl. G-CSF).

	Dependent variables			
	log (first-line treatment costs)		log(total 2-year costs)	
Independent variables	b (se)	P-value	b (se)	P-value
IPI Age category†	0.139 (0.067)	0.037	-0.110 (0.080)	0.167
IPI Stage category†	0.085 (0.075)	0.256	0.133 (0.089)	0.136
IPI LDH category†	0.132 (0.066)	0.047	0.049 (0.079)	0.533
IPI Performance status category†	0.062 (0.111)	0.579	0.247 (0.133)	0.064
IPI Extranodal sites category†	0.184 (0.087)	0.035	0.131 (0.103)	0.205
Intercept	8.778 (0.071)	0.000	9.528 (0.085)	0.000
Adjusted R^2		0.043		0.021
F-value		4.339		2.542

† values are 0 (favourable) and 1 (unfavourable). G-CSF: granulocyte colony-stimulating factor

Discussion

On the basis of data from 374 aggressive NHL patients, we performed a descriptive cost analysis on costs of first-line treatment and 2 years of follow-up, including second-line treatments. We tested if the IPI variables and the presence of B-symptoms could be used to identify groups of patients with (un)favourable cost profiles. Univariate analyses showed all 5 IPI variables and B-symptoms to be predictive of first-line treatment costs. With regard to total 2-year costs, univariate associations were shown with all variables, except for serum LDH and age. This is due to the variety in number and types of second-line therapies administered amongst younger and elderly patients, as shown in Tables 3 and 4, which causes 2-year costs to be less unequivocal than first-line treatment costs. Contrary to first-line treatment, no uniformity in second-line treatments was observed. The risk groups of the IPI system (standard index and age-adjusted index) resulting from the 5 individual variables were highly associated with first-line treatment costs and very well able to distinguish groups of patients with different cost profiles. The age-adjusted IPI was predictive of total 2-year costs, but the standard IPI was not, which we assume to be due to the reason stated above. Beyond the 5 IPI variables and the IPI risk group variables, the presence of B-symptoms was a highly significant predictor of total first-line treatment and total 2-year costs. In the multivariate analysis, this turned out to be the most significant variable, and it was included in any model resulting from step-down regression analysis.

A limitation of our study is the use of the Working Formulation as histology classification system[10]. Due to the ever evolving insight that the group NHL consists of many subentities with different prognoses, the 'Revised European-American classification of lymphoid neoplasms' (REAL), and its refined version published by the World Health Organization have now largely replaced this classification system[23, 24]. However, in the years covered by this study, the Working Formulation was the most widely used classification system and therefore the only possible histology selection system for this retrospective analysis.

Beyond this drawback, we assume to have based our analysis on a representative sample of aggressive NHL patients, as the survival of our patient group according to IPI risk groups (Figure 1b) compares very well to the survival figures of the 2031 patients on which the IPI was based[9]. Approximately 50% of our patient group underwent first-line treatment according to one of two clinical trials, but we believe this not to be a limitation, as both trials compared standard CHOP to a CHOP variant (vs. G-CSF in elderly patients, and vs. intensified CHOP+G-CSF in younger patients). Results of the trial in elderly patients have been published in the meantime and have shown no survival benefit of CHOP+G-CSF over CHOP[12]. The trial in younger patients is still ongoing. Given the design of these trials, we excluded the costs of G-CSF administered during first-line treatment from our calculation of total costs. When G-CSF prophylaxis is required, one should be considerate of additional costs of approximately €1100 per chemotherapy cycle.

In conclusion, we showed that the 5 individual IPI variables, the two IPI risk group variables, and the presence or absence of B-symptoms can be used to distinguish groups of aggressive NHL patients according to cost profiles. In addition to its traditional use in aggressive NHL, the IPI can be used to identify subgroups of patients in whom new treatment modalities may gain the relatively largest cost-effectiveness increases. We indicated that higher costs in patients with one or more unfavourable characteristics were particularly caused by hospitalisation days. New pharmaceuticals for aggressive NHL, which are successful in reducing complications and related hospitalisations, may therefore ascertain cost-effectiveness increases.

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Chapter 10. On the value of economic evaluations of non-Hodgkin's lymphoma therapy

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Abstract

Purpose. Since NHL is the most prevalent of all hematological malignancies and health care costs are rising, an increasing need for economic evaluations (EEs) of NHL treatments exists. To help hematologists and oncologists with an interest in NHL economics, we performed a literature review on the currently available NHL-EEs.

Methods. The literature review was performed using PubMed; reference lists were screened for additional publications. English and Dutch language papers were used. Only papers on studies on treatment in adults were selected.

Results. 78 publications were found, of which 40 were included. Of these, 6 EE specific methodological items were reported (study perspective, inclusion of overhead costs, mentioning of data sources, calculations based on charges or prices, sensitivity analysis, separate presentations of resource use and unit costs), enabling readers to judge the value of studies. The EEs covered 11 subjects: aggressive NHL first-line: standard therapy, hematopoietic growth factors (HGF) accompanying chemotherapy, high-dose therapy; aggressive NHL second-line: high-dose chemotherapy (HDC) with stem cell transplantation (SCT), autologous bone marrow transplantation versus peripheral blood SCT, learning effects of HDC+SCT, HGF accompanying therapy, CD34+ dose at SCT; indolent NHL: standard chemotherapy costs; trial costs, rasburicase for hyperuricaemia. Results of the publications were discussed and it was described how the 6 methodological items should be tackled in EEs.

Conclusion. Many topics remain to be appropriately studied in EEs: standard therapies, oral fludarabine, and allogeneic / autologous SCT for indolent NHL, and monoclonal antibodies (rituximab and alemtuzumab) for indolent and aggressive NHL.

Introduction

Non-Hodgkin's lymphoma (NHL) is the most prevalent of all hematological malignancies in the Western world. In the USA, the number of deaths attributable to NHL currently ranks in the top five causes of cancer related deaths[1]. NHL are among the small number of malignancies with markedly increasing incidence and mortality rates in the recent past[2]. Health care costs in developed countries have risen faster than the inflation rate since the 1960s, making economic evaluations an integral part of health care decision making[3]. Therefore, an increasing need for economic evaluations of NHL treatments exists. Since new treatments for NHL are emerging, structured information about the current ones is needed, in order to have an a priori indication of the economic impact that new treatments will have. However, economic evaluations often differ from each other, which is often particularly due to different costing methodologies applied[4]. To help oncologists and hematologists with an interest in NHL economics, we performed this literature review on economic evaluations of NHL treatments, with a focus on the way costs were calculated.

A recent study on costing methodologies was used as the framework for this review[5]. Based on the two standard textbooks for economic evaluations[6, 7], this study identified six methodological issues that should be considered when conducting economic evaluations, and which may be responsible for differences between them. Table 1 presents these 6 issues, the general recommendations on how to handle them, and the variations observed in economic evaluations. The first issue is the study's framework: has it been performed from the provider's point of view or from a societal viewpoint? In the latter perspective, patient costs and 'indirect costs' (costs of lost production due to the patient's absence from work) are additionally taken into account. The appropriate perspective depends on the study's main question. Secondly, included types of costs should have been reported: overhead costs (not primarily related to the intervention under study, like energy costs, housing costs, costs of non-medical departments), other shared costs, indirect costs, and health care costs for unrelated illness in additional years of life for the patient that were gained by the intervention under study. Overhead costs should have been fully incorporated to give account for hospital costs that are not primarily related to the intervention under study itself. Thirdly, sources of the cost data should have been clearly mentioned. At best, researchers base their unit costs (the price of one specific medical service) on data from the hospital's financial administration, like nursery salaries, doctor's wages, salaries of administrative personnel, nutrition costs, laundry costs, costs of disposables, and overhead costs. Fourthly, information on the 'valuation step' is required: were unit costs calculated from a bottom-up (calculating all resources required for delivering a service) or a top-down perspective (total cost figures obtained from financial accounts divided by the number of products delivered by a department or a medical device), were prices adjusted for market distortions, how were exchange rates applied, how were capital costs calculated, were prices or charges used as inputs, and in case of indirect costs how were time costs (e.g. volunteer time) valued? Most important in this respect is that cost calculations should not be based on charges, but on costs of actual resource consumption, as charges are known

to deviate highly from actual costs[3, 8]. If they are based on 'real costs', the result is less dependent on the health care system or type of insurance system in which context they were calculated.

Table 1. Main methodological issues within economic evaluations, general recommendations in costing guidelines and the nature of variation in applied economic evaluations, as taken from Adam et al[5].

Methodological issues	General recommendations according to costing guidelines	Nature of variations observed in applied studies
I. Framework of analysis		
a. Perspective: societal vs. provider	Societal perspective preferred, but others allowed depending on question.	Most studies used provider perspective.
b. Choice of comparator	Incremental analysis: comparing new intervention to best alternative.	Incremental analysis as well as comparing to doing nothing.
II. Types of costs included		
a. Overhead costs	Should be included, but methods of allocation are not fully discussed.	Often difficult to understand whether they were (appropriately) included.
b. Other shared costs, including allocation of labor time	Only briefly described, no validation of methods, no recommendations.	Generally not specified, different methods applied.
c. Indirect costs and inclusion of productivity gains	No agreement on whether these should be included.	Most do not include these.
d. Health care costs for unrelated illness in added years of life	(No) agreement on inclusion of future costs (not) related to current illness.	Very few included these.
III. Data collection methods		
a. Sources of cost data	No discussion of validity and reliability of data collection instruments.	Expenditure records, case registers, interviews, surveys, questionnaires, assumptions, modeling, consensus, resource use from trials.
IV. Valuation step		
a. Bottom-up vs. top-down	No discussion of methods and issues to consider in using either approach.	Both bottom-up and top-down, as well as combinations.
b. Price adjustments: price distortions	Prices should be adjusted for market distortions, but little details about method and doubt about worth of it.	Generally no discussion on whether market prices are realistic reflections of opportunity costs.
b. Price adjustments: exchange rates	Recommendation to present results in local currency.	In case of foreign currency units, often 'translation' by official exchange rates.
c. Valuation of time costs	No general recommendation about which method to use.	Several methods applied, often without mentioning their valuation.
d. Capital costs	No general recommendation about how to collect these in a valid way.	Sometimes difficult to determine whether included or not. If included, method often not specified.
e. Prices or charges	Important items should be valued on costs not charges.	Often charges without comment on how they differ from actual costs.
V. Methods of data analysis		
a. Discounting costs	Discounting should be applied.	Many did. Some not when they should.
b. Capacity utilization	Should be identified, but no guidance on how to measure capacity utilization.	Rarely reported.
c. Sensitivity analysis	Should be performed.	Not systematically done.
VI. Reporting results		
a. Ingredient approach and transparency in methods and results	Agreement on usefulness of using ingredient approach.	Rarely possible to identify physical inputs separately from unit costs.

Please notice that this is a simplified version of the original table, only presenting the main points and recommendations (readers are refered to the original publication for full details).

Fifthly, methods of data analysis should be clear: were costs discounted (costs and effects that occur later than 1 year should be discounted, reflecting people's preference for investing or having services

delivered today, rather than waiting), was capacity utilization identified (unit costs of hospital days may differ, depending on the ward's annual occupation), and was account given for uncertainty in unit costs by performing sensitivity analysis? Finally, results should be reported by using an 'ingredient approach': if both the resources required for an intervention as well as their unit costs have been reported, readers are enabled to redo calculations on the basis of their own unit costs or own assumptions about the resource use. However, as it is often impossible to present all details concerning resource use, authors should at least present details on the most important items (i.e. the most expensive ones or those with high usage frequencies)[9].

In this literature review, economic evaluations of NHL treatments in adults were searched for and categorized. Their value can be assessed on the basis of the six methodological issues. In our judgement, we placed most emphasis on the descriptive use of the publications rather than the comparative use, which is helpful for budgeting purposes: identification of the resources necessary to undertake or sustain an intervention[6].

Methods

A literature review was performed using PubMed (query 'lymphoma AND cost', last update December 31, 2003). English or Dutch language papers were selected in case the PubMed abstract appeared to indicate the containment of economic information. Only papers on treatment in adults were selected, studies on diagnostic interventions and pediatric studies were ignored. Reference lists were screened for additional publications. Additional publications from own databases were added. Articles containing (modeling studies based on) original data were included. Publications were not included in case NHL patients comprised a small part of a sample of patients with different malignancies, or if treatments diverged from current recommendations. Only full-length articles were included in the review; results of abstracts will only be mentioned shortly.

Included publications were assessed on the basis of the 6 methodological issues of economic evaluations, and the following items of Table 1 (to which the numbers refer) were recorded in Table 2:

I. Framework: the perspective (I-a) was recorded. Choice of comparator (I-b) was not recorded, given the descriptive aim of this review.

II. Types of costs: for descriptive purposes, overhead costs and other shared costs (II-a/II-b) should have been calculated appropriately, given the economic notion that *all* costs incurred in a hospital should be assigned to the services delivered. As indirect costs (II-c) and costs of unrelated diseases (II-d) have almost never been assessed in NHL economic evaluations, this was not recorded.

III. Data collection methods. Sources of the cost data (III-a) were recorded.

IV. Valuation step. The most important question is whether calculations were based on charges or 'real' prices (IV-e). If prices are calculated, they are usually calculated using a combination of bottom-up and top-down methods (IV-a) and therefore this was not recorded. We did not find specific

information on price distortions (IV-b1), hardly any information about capital costs (IV-d), and because hardly any study included indirect costs, the valuation of time costs (IV-c) was also not recorded. Exchange rates (IV-b2) are provided in this review for data presented from other studies.
V. Methods of data analysis. For descriptive purposes, the most important consideration is uncertainty regarding the results, and therefore sensitivity analyses (V-c) should have been performed. Discounting (V-a) was not recorded, as most of the studies used short-term perspectives. Capacity utilization (V-b) was never presented.
VI. Reporting results. It was recorded whether resource use and unit costs (VI-a) were reported separately.

Results

Publications

We located 78 publications, of which 38 were not included for the following reasons: no economic evaluations[10-19] (10), patient sample containing different types of malignancies, considered too heterogeneous to allow for NHL specific conclusions[20-28] (9), high dependency on local health care policy[29-32] (4), divergent from current therapy recommendations[33, 34] (2), editorial paper[35] (1), review paper on economics of stem cell transplantations for several types of (particularly hematological) malignancies[36-39] (4), review paper on autologous bone marrow transplantation only described applications in NHL patients, whereas the economic analysis focused on relapsed Hodgkin's lymphoma[40] (1), review on rituximab as third-line treatment for follicular lymphoma[41] (1), of which the economic section leaned on a study already included in our review[42], report on NHL economics[43], which considered studies already included in our review and included a cost estimate on the basis of a few of these earlier studies[44-49] (1). Five abstract (-like) publications were not included, due to the lack of required information, but their results will nevertheless be discussed below[50-54].
The 40 included publications covered 11 study subjects (Table 2) of which the overall results are discussed below. With Table 2, the value of the publications can be judged.

Table 2. Results of the literature review and assessment of the publications on the basis of six methodological issues.

Study subject First author, year	Country	I. Perspective†	II. Appropriate inclusion of overhead costs	III. Sources of cost data	IV. Unit cost type	V. Sensitivity analysis	VI. Ingredients approach: Resource use presented‡	VI. Ingredients approach: Unit costs presented
AGR1: 1st line chemotherapy								
van Agthoven 2002[60]	Netherlands	Hospital	Yes	Hospital's FinAdm	Costs	CIs	Yes	Yes
AGR1: HGF in 1st line chemotherapy								
Doorduijn 2003[64]	Netherlands	Hospital[R1]	Unclear	Hospital's FinAdm	Costs	No	Yes	No
Bobey 1998[62]	Canada	Hospital[R1]	Unclear	Hospital's FinAdm	Unclear	No	Yes	Yes
Dranitsaris 1997[49]	Canada	Society	Unclear	Hospital's FinAdm	Costs	Yes	Yes	Yes
Zagonel 1994[48]	Italy	Hospital[R1]	Unclear	Unclear	Unclear	No	Yes	Yes
Souetre 1994[63]	France	Hospital	Yes	Hospital's FinAdm	Costs	Yes	Yes	No
AGR1: High-dose therapy in 1st line								
Uyl-de Groot 1995[44]	Netherlands	Hospital[R2]	Yes	Unclear	Costs	No	Yes	Yes
AGR2: HDC with stem cell support								
Beard 2000[55]	United Kingdom	Hospital[R1]	Highly probable	Unclear	Costs (probably)	Yes	No	No
Mazza 1999[57]	Italy	Hospital[R1]	Probably	Hospital's FinAdm	Costs	No	Yes	Yes
Messori 1997[56]	Italy	Hospital[R2]	Probably	Estimates from other studies	Costs	Yes	No	No
Uyl-de Groot 1995[45]	Netherlands	Hospital[R1]	Unclear	Unclear	Costs	No	No	No
AGR2: ABMT vs PBSCT								
van Agthoven 2001[58]	Netherlands	Hospital	Yes	Hospital's FinAdm	Costs	No	Yes	Yes
Uyl-de Groot 1999[75]	Netherlands	Hospital	Yes	Unclear	Costs	No	Yes	Yes
Jerjis 1999[76]	Netherlands	Hospital[R1]	Unclear	Unclear	Unclear	No	Yes	Yes
Woronoff-Lemsi 1997[72]	France	Hospital	Yes	Hospital's FinAdm	Costs	Yes	Yes	Yes
Smith 1997[74]	USA	Hospital	Unclear	Hospital's FinAdm	Costs, charges, CtoC	Yes	Yes	Yes
le Coroller 1997[77]	France	Hospital	Unclear	Hospital's FinAdm, national price lists	Costs	Yes	Yes	No
Hartmann 1997[73]	France	Hospital[R1]	Yes	Hospital's FinAdm	Costs	No	Yes	No
Ager 1995[71]	United Kingdom	Hospital[R1]	Unclear, probably not	Unclear	Unclear	No	Yes	Yes
Uyl-de Groot 1994[78]	Netherlands	Hospital	Yes	Unclear	Costs	Yes	Yes	Yes
Faucher 1994[70]	France	Hospital[R1]	Yes	Hospital's FinAdm	Costs	Yes	Yes	No

Table 2 (continued). Results of the literature review and assessment of the publications on the basis of six methodological issues.

Study subject First author, year	Country	I. Perspective†	II. Appropriate inclusion of overhead costs	Iii. Sources of cost data	IV. Unit cost type	V. Sensitivity analysis	VI. Ingredients approach: Resource use presented‡	VI. Ingredients approach: Unit costs presented
AGR2: Learning effects HDC+SCT								
Uyl-de Groot 1999[79]	Netherlands	Hospital[R1]	Yes	Unclear	Costs	No	Yes	Yes
Freeman 1999[80]	USA	Hospital[R1]	Unclear	Patient billing records	CtoC	No	Yes	No
Meisenberg 1998[81]	USA	Hospital[R1]	Unclear	Hospital billing records	Charges, CtoC	No	Yes	No
Bennett 1995[46]	USA	Hospital[R1]	Unclear	Hospital's FinAdm	Costs	No	No	No
AGR2: HGF in 2nd line chemotherapy								
Tarella 1998[82]	Italy	Hospital[R1]	Unclear	Hospital's FinAdm	Costs	No	Yes	Yes
Lee 1998[83]	United Kingdom	Hospital[R1]	Unclear	Hospital's FinAdm	Costs	one CI	Yes	One
Souetre 1996[84]	France	Hospital	Yes	Hospital's FinAdm	Costs	Yes	Yes	No
Dranitsaris 1995[47]	Canada	Hospital	Unclear	Hospital's FinAdm	Costs	No	Yes	Yes
Bennett 1995[87]	USA	3rd party payer	Unclear	Unclear	Unclear	CI	Yes	Yes
Luce 1994[85]	USA	3rd party payer	Unclear	Hospital's billing data	Charges	No	Yes	No
Bennett 1994[86]	USA	Hospital[R1]	Unclear	Unclear	Unclear	No	Yes	No
AGR2: HDC+SCT, CD34+ dose								
Stockerl-Goldstein 2000[88]	USA	Hospital[R1]	Unclear	Unclear	Unclear	No	Yes	No
Limat 2000[89, 90]	France	Hospital	Yes	Hospital's FinAdm	Costs	Yes	Yes	Yes
Schulman 1999[91]	USA	Hospital	Unclear	Hospital's FinAdm	Costs	Yes	Yes	Yes
IND: Chemotherapy costs								
Herold 2003[94]	Germany	3rd party payer	Unclear	Published price lists, national and regional sources, previous studies	Unclear	Yes	No	Yes
Herold 2002[9]	Germany	3rd party payer	Unclear	Published price lists, national and regional sources, previous studies	Unclear	Yes	No	No
Herold 2002[92]	Germany	3rd party payer	Unclear	Published price lists, national and regional sources, previous studies	Unclear	No	No	Yes
Sweetenham 1999[42]	United Kingdom	Hospital	Probably	Hospital's FinAdm	Costs	Yes	Yes	Yes

Table 2 (continued). Results of the literature review and assessment of the publications on the basis of six methodological issues.

Study subject First author, year	Country	I. Perspective†	II. Appropriate inclusion of overhead costs	III. Sources of cost data	IV. Unit cost type	V. Sensitivity analysis	VI. Ingredients approach: Resource use presented‡	VI. Ingredients approach: Unit costs presented
Trial costs								
van Agthoven 2002[60]	Netherlands	Hospital	Yes	Hospital's FinAdm	Costs	CIs	Yes	Yes
Rasburicase for hyperuricaemia								
Annemans 2003[98]	Belgium	3rd party payer	Unclear	Published national sources	Costs	Yes	No	No

† The difference between the hospital perspective and the 'third party payer' perspective is the usual excusion of facility costs (e.g. clinic, office), and utility costs (e.g. telephone, electricity) in the latter perspective[3].
‡ Implying that at least the main indicator(s) of resource use should have been mentioned.
R1: Perspective was not specifically mentioned, but was interpreted from the cost categories included or the description of the cost calculation methodology.
R2: Authors mentioned a social perspective, but study only included costs as calculated from a hospital perspective.
ABMT: autologous bone marrow transplantation, AGR1: first-line therapy for aggressive NHL, AGR2: second-line therapy for aggressive NHL, CtoC: estimated costs from charges using cost to charges ratios, CI(s): confidence interval(s), FinAdm: financial administration, HDC: high-dose chemotherapy, HGF: hematopoietic growth factors, IND: indolent lymphoma, (PB)SCT: (peripheral blood) stem cell transplantation.

Of six subjects, costs from the most recent studies are presented in Tables 3-5. Most of these studies presented their costs in 1998 Euros and therefore, this currency and price level was used in all tables. Table 3 presents aggressive NHL costs: first-line standard chemotherapy, CHOP vs. CHOP+HGF, and PBSCT for second-line use, and it also covers the subject 'trial costs'. These costs were all calculated according to the same methodology by the same research group, including an appropriate inclusion of overhead costs, and are therefore assumed to be comparable and to be reflecting 'full' actual treatment costs. Tables 4 and 5 both relate to indolent NHL, and are also assumed to be proper estimations of full treatment costs. Notice that costs on the following subjects from Table 2 on aggressive NHL have not been presented (+reason): HDC in first-line (abandoned concept), HDC with stem cell support (2 studies with estimated costs[55, 56] on the basis of other publications and 1 small study[57], actual costs are already reflected in Table 3[58]), learning effects of HDC+SCT (assumed to have been incorporated in the most recent study[58]), HGF in second-line (small studies, doubt about general validity, see below), CD34+ dose at HDC+SCT (refinement of PBSCT costs).

First-line therapy for aggressive NHL

First-line standard chemotherapy for aggressive NHL

For aggressive NHL, standard first-line therapy has been CHOP chemotherapy ever since 1976[59]. One publication on its costs was found[60] (an earlier study focused on selected patients[44], see 'High-dose therapy in the first treatment line'). This study (Table 3) focused on cost differences between trial and non-trial treatments. It showed that costs of diagnosis, treatment and follow-up were in the same order or at worst only a little higher in case of trial treatments (however, no tests of significance were performed), because of somewhat higher costs of diagnostics and the mean number of chemotherapy cycles was higher in elderly patients. This finding is consistent to an earlier survey on current practice in diagnosis and treatment of aggressive NHL in the Netherlands[61], which showed that chemotherapy was ceased earlier or doses were reduced faster in case of leucocytopenia or thrombocytopenia.

Hematopoietic growth factors (HGF) accompanying first-line standard chemotherapy

Three small studies suggested that adding prophylactic HGF to standard chemotherapy would lead to a more cost-effective treatment as compared to standard chemotherapy without HGF, particularly in elderly patients[48, 49, 62]. A larger 1994 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 HGF led to lower costs, given a lower number of infections and less hospital days[63]. However, costs of lenograstim itself were left out of consideration. The cost benefit is no longer present if HGF costs are added. A recent large Dutch prospective randomized clinical trial in elderly NHL patients showed prophylactic addition of HGF to standard CHOP not to be a cost-effective policy. Treatment costs increased with almost 60% (see Table 3), while response and survival rates were unchanged[64].

Table 3. Costs of first- and second-line therapy for aggressive NHL as based on Dutch studies (1998 Euros). SLP = standard local practice, PBSCT = peripheral blood stem cell transplantation.'Transplant related' comprises costs of harvesting, freezing, and defrosting PBSCT transplant. Group 1 received CHOP chemotherapy, group 2 received CHVmP/BV (cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine) chemotherapy.

	Hospitalization	Outpatient visits	Day care center use	Radiation therapy	Laboratory diagnostics	Other diagnostics	Blood components	Cytostatics	G-CSF	Antibiotics	Other medication	Transplant related	Total costs	Total costs excl. hospital days	Total costs excl. G-CSF	Total costs excl. hospital days & G-CSF
First-line standard chemotherapy[60]																
Diagnostic phase trial group 1 <65	2539	153	-	-	983	999	102	-	-	40	21	-	**4837**	2298	-	-
Diagnostic phase trial group 2 <65	2464	211	-	-	950	909	-	-	-	-	24	-	**4560**	2096	-	-
Diagnostic phase SLP group <65	1851	132	-	-	818	774	-	-	-	-	-	-	**3576**	1725	-	-
1st line treatment trial group 1 <65	2259	198	708	-	672	855	299	2069	3006	152	22	-	**10239**	7979	7232	4973
1st line treatment trial group 2 <65	3188	272	1348	171	1026	988	653	2184	674	98	83	-	**10683**	7495	10009	6821
1st line treatment SLP group <65	3937	246	506	-	500	472	72	1791	863	38	50	-	**8473**	4535	7610	3672
Follow-up (<1 yr) trial group 1 <65	488	253	-	335	319	412	19	-	-	-	-	-	**1825**	1337	-	-
Follow-up (<1 yr) trial group 2 <65	1792	464	-	491	496	601	9	-	-	25	14	-	**3893**	2100	-	-
Follow-up (<1 yr) SLP group <65	1835	276	-	575	590	739	-	-	-	-	-	-	**4015**	2180	-	-
Diagnostic phase trial group ≥65	3722	149	-	-	1004	1106	-	-	-	14	6	-	**6000**	2278	-	-
Diagnostic phase SLP group ≥65	2120	169	-	-	776	848	-	-	-	-	-	-	**3914**	1794	-	-
1st line treatment trial group ≥65	3690	278	603	-	764	1210	122	1727	2954	229	96	-	**11673**	7983	8719	5029
1st line treatment SLP group ≥65	3805	184	304	6	482	560	30	1336	842	28	86	-	**7663**	3858	6821	3016
Follow-up (<1 year) trial group ≥65	1142	313	-	51	532	564	-	-	-	-	21	-	**2623**	1482	-	-
Follow-up (<1 yr) SLP group ≥65	2988	257	-	924	410	432	-	-	-	-	-	-	**5010**	2022	-	-
Trial CHOP vs CHOP+G-CSF[64]*																
1st line treatment CHOP†	4433	598	665	263	746	1198	531	1638	55	373	307	-	**10805**	6373	10750	6318
1st line treatment CHOP+G-CSF†	5029	517	540	351	681	1118	401	1557	6138	172	341	-	**16795**	11766	10657	5628
Trial PBSCT‡ 2nd line therapy[58]*																
Induction chemotherapy	6340	295	137	162	806	504	927	1449	296	202	345	-	**11464**	5124	11168	4828
Leukapheresis + follow-up	1505	210	34	-	271	313	387	-	851	124	42	1865	**5602**	4097	4751	3246
PBSCT hospitalisation	9550	111	-	-	783	604	1722	829	13	923	665	186	**15386**	5836	15373	5823
Follow-up (<3 months)	327	456	227	112	207	299	503	-	-	8	1	-	**2141**	1814	-	-

† these costs only relate to the period of treatment itself.
‡ ABMT results of this trial have not been shown, given the standard being PBSCT now. Induction chemotherapy comprised the DHAP-VIM-DHAP scheme.
* Costs were originally presented in 1997 Euros, but were upgraded to 1998 Euros by multiplying them by 1.025, as recommended by Statistics Netherlands (CBS).

High-dose therapy in the first treatment line

In a dated Dutch prospective trial, slowly responding patients with aggressive NHL were randomized to standard CHOP +/- autologous bone marrow transplantation (ABMT)[44]. CHOP was ten times less expensive as compared to CHOP+ABMT (US$ 3,118 vs US$ 34,445, 1992 price level). Moreover, survival was not increased by CHOP+ABMT, whereas the number of quality adjusted life years gained was lower. This study showed that the cost-effectiveness of standard first-line chemotherapy was not improved by adding high dose therapy. One small UK study, only published as an abstract, confirmed this result[50].

Rituximab addition to standard chemotherapy

Short-term perspectives look promising since the introduction of rituximab, a monoclonal antibody targeted against the B-cell specific antigen CD20 present in approximately 80% of all patients with diffuse large B-cell lymphoma. Coiffier and colleagues performed the first phase III clinical trial of CHOP vs. CHOP+rituximab (R-CHOP) in elderly patients showing a higher complete remission percentage and a better survival with R-CHOP[65, 66]. A recent American study showed no survival benefit of R-CHOP over CHOP, but this study can not be compared to the first one, given a difference in design (second randomization to rituximab maintenance therapy or nothing in case of complete or partial response)[67]. One paper concluded that for the time being CHOP remains the standard treatment for aggressive NHL, and that R-CHOP may be justified for patients who meet the inclusion criteria as used in Coiffier's trial[19]. In a recent position paper, rituximab was concluded to be a cost-effective addition to CHOP chemotherapy[18]. The study on which this statement was based (abstract only) concluded therapy related costs to be higher with R-CHOP, but the cost-effectiveness was considered to compare favorably with other oncology treatments in widespread use[53]. It should be noticed that cost-effectiveness estimations in this study were based on Coiffier's trial, which has been criticized for its relatively poor response in conventionally treated patients. Earlier cost-effectiveness estimations from the same group based on an interim analysis of Coiffier's trial had already shown similar results[54]. Another cost-effectiveness estimation (only published as an abstract), which additionallly took costs of possibly applied salvage therapies for younger patients into account, concluded that while R-CHOP is slightly more effective, CHOP is less expensive despite inclusion of salvage therapy and SCT, and that CHOP plus salvage and SCT remains a cost-effective option[51]. An appraisal of the UK's National Institute for Clinical Excellence (NICE) concluded rituximab to be cost-effective relative to CHOP used alone, based on two modelling studies from rituximab's manufacturer (Roche) and NICE's assessment group[52]. However, it should be kept in mind that these data on rituximab's cost-effectiveness were all based on modelling studies relying on assumptions and data from other studies. Therefore, more studies primarily containing patient data based calculations need to be performed before any definite conclusions can be drawn on the cost-effectiveness of R-CHOP over CHOP.

Second-line therapy for aggressive NHL

High-dose chemotherapy with stem cell support

For younger patients with refractory or recurrent NHL, high-dose chemotherapy (HDC) with stem cell support constitutes a (second) chance of curation in case of sensitivity to second line chemotherapy. There is however only limited evidence for the superiority of HDC with stem cell support over conventional chemotherapy[35, 38-40]. For recurrent or refractory NHL, this application is based on the PARMA trial, in which (only) 109 patients were randomised[68]. Given its results, this trial has turned HDC with stem cell support into a worldwide standard second line treatment for chemosensitive patients with refractory or recurrent NHL[69].

The cost-effectiveness of HDC with stem cell support over conventional chemotherapy has never been demonstrated convincingly. To do so, a prospective randomized study would be necessary[38], but given the treatment's established place, such a study will not be performed anymore[35]. Costs of HDC with stem cell support are high compared to the former conventional treatment[45]. Nevertheless, given the favorable results, several publications argue HDC with stem cell support for recurrent or refractory NHL to be relatively affordable and the cost-effectiveness is supposed to be relatively favourable[55-57].

Autologous bone marrow transplantation (ABMT) versus peripheral blood stem cell transplantation (PBSCT)

The majority of NHL economic evaluations have been focused on the comparison of PBSCT and ABMT as supportive therapy following HDC for recurrent or refractory NHL. As a result, convincing evidence has been provided for the superiority of PBSCT over ABMT, which has been confirmed by four reviews[36-39]. All studies agree on the causes: PBSCT is less expensive because PBSCT patients demonstrate a faster hematologic recovery. As the duration these patients are at risk for infections is shorter, they are hospitalized shorter and require less blood transfusions[36, 58, 70-78]. The last and largest prospective randomized trial demonstrating PBSCT's superiority confirmed these cost advantages, and added a quality-of-life comparison[58]. The 'Rotterdam Symptom Checklist' demonstrated several differences in favor of PBSCT patients. PBSCT costs in this study (from induction chemotherapy up to 3 months of follow-up) were 15% lower than ABMT costs, and are shown in Table 3.

Learning effects

Learning effects may have influenced costs of HDC with stem cell support in the course of time. Beyond the increased cost-effectiveness resulting from switching from ABMT to PBSCT, several studies showed decreased costs over time as a result of a shorter hospitalization and less blood transfusions[46, 79]. One study showed decreased costs as more parts of the therapy were administered on an outpatient basis[80], and in another one similar suggestions were stated[81].

Hematopoietic growth factors (HGF) accompanying high-dose chemotherapy

Economics of HGF administration following PBSCT or ABMT have been extensively studied. In general, HDC+PBSCT is found to be more cost-effective in case of post-transplantation HGF support[47, 82-85]. However, the studies were usually small (with the exception of one study not more than 20 patients in the HGF arm) and in most of them no statistical tests were performed. Moreover, differences were often modest, and therefore the extent to which standard post-transplantation HGF support is cost-effective is probably highly dependent on country or hospital. A 1994 study showed post-transplantation HGF support to lead to savings in an American hospital, whereas it did not in a French hospital[86]. Although based on rough cost estimates and on results published before[85, 86], a 1995 study showed that HGF support led to shorter hospitalisations and therefore to lower costs in four out of six hospitals participating in phase III clinical trials, whereas it did not in the other two hospitals[87].

The CD34+ (stem cell) dose

With regard to HDC+PBSCT the influence of the CD34+ dose on the cost-effectiveness of the SCT has been studied. One study showed that 'poor mobilizers' (patients in whom less than $2x10^6$/kg CD34+ cells were harvested) generated higher costs as compared to patients in whom $>2x10^6$/kg CD34+ cells were harvested. The higher costs were mainly generated during the post-transplantation traject[88]. Other studies showed that with a dose higher than $5x10^6$/kg, less fever occured and duration of antibiotics treatment was shorter, which is expressed by a faster hematologic recovery. This necessitated less blood transfusions and resulted into a faster discharge. Reinfunding a dose of $\geq 5x10^6$/kg turned out to be the most cost-effective strategy[88-91].

Indolent lymphomas

Costs of regular chemotherapy schemes

For indolent NHL, many treatment regimens are available, ranging from a wait-and-see policy via several chemotherapy schemes to autologous or allogeneic SCT. So far however, only two economic evaluations have been performed. The first compared the costs of CHOP, fludarabine, and rituximab[42]. The authors suggested these therapies to be of equal effectiveness (remission percentage and remission duration) and therefore, a cost analysis was supposed to be sufficient to determine the most cost-effective treatment. Fludarabine was the most expensive treatment (€ 14.809, see Table 4), not only because of the high costs of fludarabine itself, but also because of the high administration costs (every cycle requiring 5 consequent days of using day care facilities for intravenous administration). CHOP cost € 10.653 whereas rituximab brought along costs of € 8.984. Drug costs were the highest within the rituximab scheme, nevertheless these were compensated by savings on administration costs and the low costs of treating adverse events. Therefore, the authors suggested rituximab to be a cost-effective alternative in comparison to existing treatment modalities for indolent

NHL. However, this conclusion was slightly put into perspective in a review on rituximab for stage III/IV follicular lymphomas[41]. The study was criticized for its supposed underestimation of rituximab's adverse event rate, and therefore for the reported total costs. The cost analysis methods were criticized, and the evidence used to demonstrate equal effectiveness of the three treatment modalities was found to be weak. Nevertheless, the authors of the review assumed that in a worst-case scenario, the costs of rituximab would be comparable to the costs of many other treatment schemes used for indolent NHL. Moreover, the lower costs of rituximab as compared to the other treatment modalities were found to be stable in a sensitivity analysis that was performed later. However, for the health care system as a whole, rituximab was concluded not to lead to savings, as it does not replace any of the existing treatments.

Table 4. Costs of frequently applied treatments for relapsed indolent NHL[42].

	Costs as converted to 1998 Euros		
	Fludarabine	CHOP	Rituximab
Inpatient stay	884	368	408
Outpatient visit	2655	674	378
Drug costs	6649	1529	7596
Tests	257	621	439
Adverse events	4363	7460	161
Total	**14809**	**10653**	**8984**

Costs as originally published were converted to 1998 Euros to enhance comparability with Tables 2 and 3. The average British pounds to Euro exchange rate (1.4776) during 1998 as calculated by the Pacific exchange rate service of the Sauder School of Business at the University of British Columbia (http://fx.sauder.ubc.ca/data.html) was used for this conversion.

The most recent study on the indolent NHL costs compared costs of CHOP, CVP, and fludarabine, and separate analyses were performed on toxicity costs and drug delivery costs[92-94]. Unfortunately, this study may be criticized for its cost calculation method, in which the costs of only 1 cycle of chemotherapy were calculated and extrapolated to the entire course of treatment. Nevertheless, this study nicely showed the setting of the therapy (inpatient or outpatient) to highly influence total costs (Table 5). Considerable savings are possible in case of shifting from inpatient to outpatient treatments. Unfortunately, costs of adverse events were assumed to be the same within inpatient and outpatient settings. It was shown that costs of comparable treatments may highly differ depending on country (Table 5).

Like many others, this study showed that the costs of treatment are not simply constituted or mainly influenced by the costs of the medication itself, but that treatment of adverse events is of paramount importance[92, 93]. The toxicity study showed that costs of toxicity with conventional treatment regimens are substantial, and up to 20 times greater than drug acquisition costs[93].

Overall results were presented most clearly in the original publication[92]. The third publication[94] left costs of adverse events (specified in the second publication[93]) out of consideration, which makes it less valuable as a description of full costs related to chemotherapy administration. Unfortunately, the three publications all suffer from the lack of the presentation of resource use numbers.

Table 5. Costs of frequently applied treatments for relapsed indolent NHL: breakdown of the average cost of treatment per patients (1998 Euros) into administration, drug acquisition, and adverse event costs for in-patient and out-patient administration for 6 cycles, and breakdown of the total adverse event costs during these cycles, as taken from Herold et al[92, 93].

Regimen / country	In-patient				Out-patient					Breakdown of total adverse event costs					
	Administration costs	Drug acquisition costs	Adverse event costs	Total costs	Administration costs	Drug acquisition costs	Adverse event costs	Total costs	Percentage of patients receiving chemotherapy as in-patients	Neutropenia and fever, infection	Nausea, vomiting	Anaemia	Thrombocytopenia	Other	Total adverse event costs
CHOP															
Canada	5639	2217	5036	12892	2187	2216	5036	9439	12%	3873	142	42	95	884	5036
Germany	5512	1706	2515	9733	444	1706	2515	4664	46%	942	310	869	87	307	2515
Italy	3781	470	2179	6430	335	929	2179	3445	19%	1625	191	278	81	4	2179
CVP															
Canada	7198	162	3252	10612	2847	162	3252	6261	14%	1452	138	61	776	825	3252
Germany	8088	361	2658	11107	506	361	2658	3525	51%	1429	404	570	223	32	2658
Fludarabine															
Canada	8738	3931	1273	13942	3338	3931	1273	8542	7%	1149	97	5	22	0	1273
Italy	9166	3861	4908	17940	770	7723	4908	13401	38%	1655	1833	595	659	166	4908

Conversion rate from local currency to € (April 1998): Canada, 0.672; Germany 0.511; Italy, 0.000517.

Costs of trial treatments

It is often suggested that trial treatments lead to higher costs, particularly because of diagnostic tests that have to be performed on predefined points of time. However, a small American study in several malignancies showed no difference in costs between trial treatments and standard local practice (SLP) treatments[26]. A large American study in patients with different neoplasms confirmed this conclusion[27].

With regard to the relation of the costs to the effects, it has been suggested that trial treatments in oncology may lead to improved results as compared to SLP treatments[12]. After all, subjecting clinicians to rigorous rules of trial protocols may lead to a more adequate, more timely or more stringent monitoring of patients. In NHL, earlier studies support this suggestion: particularly the staging of elderly lymphoma patients appeared to be incomplete in some cases[95, 96].

In the discussion of the before quoted Dutch study on first-line NHL treatment[60], which showed the costs of trial treatments and SLP treatments to be in comparable ranges, it was also questioned if trial treatments may even be a cost-effective alternative to SLP treatments[60]. For example, the observed dose reduction in elderly patients treated according to SLP is strongly discouraged because of worse treatment results[97]. Moreover, trial treatments could also lead to savings. For example in the Dutch

study, trial patients underwent chemotherapy on an outpatient basis more often as compared to their SLP counterparts[60]. Likewise, trials do not necessarily bring along higher costs for insurers or hospitals in case additional costs are paid by pharmaceutical companies.
For NHL specifically, more research is needed before definite conclusions can be drawn on this topic.

Other topics
A European study concluded rasburicase (recombinant urate oxidase) to be an economically attractive new option in the treatment of hyperuricaemia in hematological cancer patients[98].

Discussion

This review was written with the aim to help oncologists and hematologists who are searching for economic evaluations of NHL treatments and wondering how they should be valued. Our main concern has been the descriptive use of economic evaluations: did they present their results in such a way that others can use them for own (budgeting) purposes, or in other words did they present a clear identification of the resources required to deliver a certain intervention and the costs of these resources? The rationale behind this question is that to our belief, beyond comparative purposes, economic evaluations should provide basic information for future analyses, thereby enabling clinicians to incorporate economic information in their decisions, and improving possibilities to estimate the economic impact of new treatment alternatives.
From six methodological issues in economic evaluations[5], we chose the most important indicators for this descriptive value of studies. Valuing the publications on the basis of these issues is rather simple: the higher the frequency of 'yes' (issue II), 'hospital's financial administration' (III), 'costs' (IV), 'yes' (V), and 'yes/yes' (VI) in Table 2, the better. Most studies used the hospital perspective (item I), but we do not consider this as a drawback given our purposes. Moreover, there is no agreement if indirect costs should be included at all (in order to obtain a societal perspective)[5]. The high frequency of 'unclear' and 'probably' at 'appropriate inclusion of overhead costs' (at item II in Table 2) indicates a drawback of many publications. It does not necessarily indicate a drawback of the studies themselves, as they might have been included, but it certainly indicates a drawback of the way of presentation. Table 2 further indicated that many publications suffer from the lack of sensitivity analysis (item V). At least confidence intervals of the main results should be presented. In Tables 3-5, we presented costs on the main topics from the most recent studies, which we all considered to reasonably comply with the 6 items and to appropriately reflect full hospital costs.
Indirectly, Table 2 also indicates that still many NHL therapies have not been subjected to economic evaluations yet. For example, costs of relatively simple and cheap (often first-line) therapies for low-grade lymphomas (like radiotherapy, chlorambucil +/- prednisone, but also the watchful waiting strategy) have not been published yet, whereas these should be comparators for costs of new

treatments. The expensive allogeneic SCT procedure should also be subjected to an economic evaluation, as this might be the only curative treatment option for low-grade follicular NHL. Although many studies have focused on autologous SCT for aggressive lymphomas, the cost-effectiveness of this procedure as salvage therapy in young low-grade NHL patients still remains to be answered. Given the latest developments, concise economic questions relate to the application of monoclonal antibodies targeted against the CD52 (alemtuzumab, for low-grade lymphomas) or CD20 antigens (rituximab, for both low- and high-grade lymphomas). Because of the high costs of these therapies, the economic question is amongst the most important ones, particularly for rituximab, of which some already believe that this should not be withheld to any aggressive NHL patient in addition to the standard CHOP therapy[18]. Another interesting economic question is the recent introduction of oral fludarabine, which probably highly favors the cost-effectiveness of low-grade NHL treatment, given the removal of 5 consecutive days of using day care facilities at each intravenously administered cycle of fludarabine.

Future publications on economic evaluations on NHL treatments should provide full details on the six methodological items mentioned in this review, thereby preferably tackle them in the recommended ways.

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Conclusions

Following the central question, this thesis focused on economics of diagnosis, treatment and follow-up (including second-line treatments) of aggressive non-Hodgkin's lymphoma (NHL) in the Netherlands. The emphasis has been placed on adequately estimating the actual cost level, which is important for budgeting purposes, determining appropriate reimbursement amounts, reimbursement decisions per se, and indicating opportunities for efficiency improvement. To achieve this aim reliably, all studies were based on real patient data. Another main issue has been the difference between treatment according to 'standard local practice' (SLP) and treatment within a randomised clinical trial (RCT) with rigorous protocols exactly prescribing times and types of diagnostic and therapeutic modalities to be applied.

As a basis for all analyses, the current situation with regard to management of aggressive NHL patients was mapped by making an overview of available treatment guidelines and a survey among haematologists. Agreement on the first-line treatment was shown, but no agreement existed on second-line treatments (except for high-dose chemotherapy followed by stem cell transplantation in younger patients). Moreover, it was shown that in daily clinical practice, diagnostic tests were sometimes left undone, and chemotherapy was stopped or reduced sooner in case of thrombocytopenia or leukocytopenia. Many of the surveyed haematologists said to include patients with aggressive NHL in RCTs, although in practice the participation rate is rather low according to the trial office of the Dutch Working Group on Adult Haemato-Oncology (HOVON). This inconsistency might be due to the selection of surveyed haematologists. Factors hindering trial participation were lack of time, logistic problems, and the ethics committee procedure.

Consequently, the costs of the initial diagnostic phase, costs of the standard CHOP and CHvMP/BV first-line treatments, and costs of one year disease-free follow-up were calculated. The study yielded first insights into costs within RCT and SLP settings. Basically, the costs were within comparable ranges, although costs of diagnostics appeared to be somewhat higher within the RCT settings. CHvMP/BV chemotherapy was more expensive than CHOP standard chemotherapy, because of an additional infusion of cytostatics at mid-cycle.

With regard to second-line treatment for younger patients who showed chemotherapy-sensitivity, in an RCT, peripheral blood stem cell transplantation (PBSCT) was shown to be superior to autologous bone marrow transplantation (ABMT) as rescue therapy following high-dose chemotherapy. PBSCT was associated with a faster engraftment of neutrophils and thrombocytes, and fewer transfusions of red blood cells and platelets were required. The number of days with fever and the number of days with intravenous antibiotics in patients with fever were significantly lower in the PBSCT group. Beyond these advantages, PBSCT was associated with lower costs and a better quality of life compared to ABMT. The quality of life of younger patients with relapsed or refractory aggressive NHL turned out to be comparable to the quality of life of other cancer patients.

From a literature review, it became clear that not all the results obtained with standard CHOP in RCTs during the past 25 years are comparable to each other. Moreover, differences within the outcome measures (overall response, complete response, 2-year overall survival) could not unanimously be explained by differences in patient and treatment characteristics. Therefore, not all RCT results are representative of results obtained in daily clinical practice and generalisation of the absolute trial result should only be done after careful scrutiny of patient-, disease-, and study characteristics. Most important in this respect were age of patients, histology of the NHL, and, with regard to the studies, sample sizes, which comprised important directions for the consequent studies.

In a single-centre study, it was shown that the survival of patients with aggressive NHL did not differ during the years 1994-2001 according to RCT treatment or SLP treatment. In this centre, SLP and RCT patients received equally effective therapy. Nevertheless, RCT inclusion was recommended because of strict monitoring and promising future developments for NHL patients. Together with the comparable cost data within RCT and SLP settings, presented earlier, this study led to a study on both costs and effects in larger patient groups.

In this next study, costs as well as survival were concluded to be comparable among younger RCT and SLP patients, which implies that RCT costs and effects in younger aggressive NHL patients can be representative of SLP costs and effects. In elderly patients, the survival was also identical, but the costs of the first-line treatment were approximately 11-13% higher in the case of RCT treatment. These somewhat higher costs were however relativised in the discussion section of this study, primarily on the basis of the conclusion that diagnostic tests are applied more properly in RCT settings, which may have crucial implications for these patients. As some doubts were raised about our elderly patients RCT group, it may in the end be plausible that in elderly patients, RCTs will generally result in a somewhat higher survival, without contributing to importantly higher costs.

A detailed presentation of costs of all parts of the disease course (up to two years) was given in the consequent study, which confirmed that there is no agreement on second-line treatments and that the costs occurring after the first-line treatment are highly dependent on a relatively small number of patients and on the types of treatments applied in these patients. Costs of second-line treatments were shown to be highly variable. The study focused on factors influencing the treatment costs and it was shown that the International Prognostic Index for Aggressive NHL (IPI), which has been used for years to predict survival, is also very predictive of total treatment costs. Also, the presence of B-symptoms (fever, night sweats, weight loss) turned out to be a very significant cost determinant.

Finally, the current state of affairs with regard to economic evaluations in NHL, next to the information provided in this thesis, was presented. This literature review grouped all available publications according to the different topics that have been studied in NHL economic evaluations and it valued these evaluations on the basis of their methodological merits. Topics studied in NHL economic evaluations were: standard first-line therapy for aggressive NHL, haematopoietic growth factors accompanying first-line chemotherapy for aggressive NHL, and high-dose first-line therapy for aggressive NHL. With regard to second-line therapy for aggressive NHL, the following topics have

been subjected to economic evaluations: high-dose chemotherapy (HDC) with stem cell transplantation (SCT), autologous bone marrow transplantation versus peripheral blood SCT, learning effects of HDC + SCT, haematopoietic growth factors following SCT, CD34+ dose in the SCT procedure. For indolent NHL, costs of standard chemotherapy have been calculated. Finally, studies were performed on trial costs, and rasburicase for hyperuricaemia. Methodological points that should be awarded and addressed properly in (NHL) economic evaluations are: appropriate study perspective, appropriate inclusion of overhead costs, basing unit costs preferably on data from the hospital's financial departments, basing unit costs preferably on real prices (instead of charges), performing sensitivity analyses, and separate presentations of both resource use and unit costs.

In the introductory chapter, it was furthermore mentioned that this thesis was also meant to contribute to the knowledge with regard to quality as well as effectiveness of care outside the context of RCTs, because only little is known about 'daily clinical practice'. The fact that little is known about care outside RCTs is actually quite understandable, because for e.g. pharmaceutical companies there is less need for cost-effectiveness studies once their pharmaceuticals have successfully passed the reimbursement decision process. Effectiveness of care in SLP for aggressive NHL patients was already described above. Chapter 8 in particular yielded insights in the quality of care outside an RCT context. With regard to the therapy itself, almost no differences in treatment between RCT and SLP appeared to exist, except for the somewhat higher percentage of elderly SLP patients for whom dose reduction was applied (not significant), a result that is consistent to the findings of the survey presented in Chapter 2. Differences between RCT and SLP however were shown with regard to diagnostic modalities. The survey in Chapter 2 had already shown that diagnostic tests were sometimes left undone in SLP and that restaging was not always done adequately. Chapter 8 confirmed that in SLP, particularly radiological imaging is not always performed according to 'best practice recommendations'. This is an important finding, because these imaging studies are or should be performed at 'clinical decision making moments', i.e. whether or not to continue the ongoing treatment or to switch to alternative therapy. This might avoid unnecessary and ineffective treatment in non-responding patients. Furthermore, following strict trial protocols might circumvent the occurrence of misconceptions with regard to diagnostic tests. Sometimes in SLP, it is suggested that for example the unpleasant bone marrow biopsy might be left undone in elderly patients, because the patient is already known to have stage IV NHL, and the result of the bone marrow biopsy will therefore not change staging or treatment policy. However, the ignorance about a bone marrow localisation of NHL might lead to the erroneous conclusion that the patient has reached a complete remission, with the possibly fatal implication of not administering a second-line treatment or consolidation radiotherapy. In conclusion, strict trial protocols ensure a higher quality of care with more rigorous patient monitoring compared to SLP settings. The fact that Chapter 2 showed that the actual rate of RCT participation appears to be low implies that there is still a lot to gain in practice.

Long-term differences between trials and standard local practice

One of the most important conclusions regarding the representativeness of costs generated by RCT patients for the costs generated by patients in SLP was drawn in Chapter 8. However, one might object to its conclusion by stating that only costs of first-line treatment were considered and that all later costs were ignored. However, this was explicitly done on purpose for the following reasons. Firstly, the RCTs considered in this study specifically focused on the first-line treatment and therefore, the 'generalisability question' should also be focused on this part of a patient's treatment course. Secondly, the survival was comparable among the RCT and SLP groups as was the ratio of responders to no-responders. This actually implies that all what happens after the first-line treatment can be considered to be independent of initial treatment group (i.e. RCT or SLP). Thirdly, in Chapter 9 the costs of 'all what happens after the first-line treatment' were shown to be highly variable. Some of the second-line treatments were shown to be very expensive (also demonstrated in Chapters 4/5), whereas others were not, while on the same time it also turned out that these relatively divergent costs were only generated by a small number of patients. This implies that only the slightest imbalance in the distribution of patients who receive second-line treatments and the types of treatments that they undergo might be responsible for large differences in costs among the several groups. Including these costs in an analysis that was meant to test representativeness of RCT for SLP with regard to a first-line treatment might therefore easily lead to erroneous conclusions. Fourthly, the third argument is also on medical grounds assumed to be highly valid for the field of aggressive NHL, in which a marvellous harmony exists on the first-line treatment, but not at all on consequent treatment lines (except for the application of stem cell transplantations for younger patients), as was shown in Chapter 2. Fifthly, it has to be kept in mind that the cost difference of 11-13% demonstrated for elderly patients in Chapter 8, on the basis of the first-line treatment costs only, in fact represents a 'worst-case scenario'. This statement is based on nothing more than a plain arithmetic ratio. Including costs that occur later will only diminish this difference, and therefore the influence on the cost-effectiveness ratio will always be 11-13% at the maximum (provided that treatments are comparable to those that were studied in this thesis). For the elderly patients, this can be demonstrated as follows (younger patients are left out of consideration, as their similar costs and survival imply that the cost-effectiveness ratios are equal and independent of trial context). Chapter 8 demonstrated the first-line treatment costs in elderly patients to be € 10018 (SLP) and € 11273 (RCT), respectively (Chapter 8, Table 6, column MPA3). In this calculation, follow-up costs are assumed to be equal among RCT and SLP groups, for the reasons set out above. From Chapter 9 it can be deduced that the mean discounted follow-up costs (up to two years) were € 7924 in elderly patients. This implies that the total discounted 2-year costs for elderly patients were € 17942 (SLP) and € 19197 (RCT), respectively, which is a difference of € 1255, or only 7%, whereas the initial difference was concluded to be approximately 11-13%. The relative difference will of course decrease further when longer-term perspectives are applied.

Policy implications

In the next section the implications or lessons of this thesis for health care researchers and for health care policy, at the level of the individual patient-doctor relationship and at higher levels will be reasoned.

Recommendations for clinical practice guidelines

The results of the analysis of current management strategies for aggressive NHL and the consequent survey have been shown to be useful in the development of national clinical practice guidelines for NHL, which will be issued in 2004. The aim of this guideline was to 'streamline' diagnosis and treatment of NHL in the Netherlands. For example, the survey had shown variety in second-line treatments, shortcomings with regard to restaging procedures, and therapies that were sometimes reduced or stopped too soon in case of complications. In such a situation, a national guideline may contribute to optimising the care process. This should finally result in the most adequate management of all patients, irrespective of the hospital to which the patient turns. The observation of new therapeutical and diagnostic modalities appearing on the scene[1] demonstrates the importance of frequent future updates of this guideline. Our survey has been shown to be a useful instrument to quickly analyse bottlenecks, shortcomings and inconsistencies in the current management of patients. Such a survey can be repeated in the near future to show points that ask for amendments in the guideline. The Internet might contribute to this, as surveys via this medium are an efficient and affordable way of quickly gathering the required information.

Recommendations for cost-effective practices

For first-line therapy of NHL, some haematologists apply CHvMP/BV chemotherapy as an alternative to CHOP. Although it was not one of the major conclusions of this thesis, Chapter 3 showed CHvMP/BV to be a more expensive regimen than CHOP, which is quite understandable, given the additional infusion of cytostatics within this scheme at mid-cycle. CHvMP is administered at day 1, and the patient has to visit the hospital additionally at day 15 to undergo infusion of bleomycin and vincristine (BV). This might also cause additional burden to patients, although this has never been investigated. Moreover, it asks for additional capacity of day care centre facilities, which may limit treatment possibilities for other patients.

Chapter 3 demonstrated the major impact of treatment setting on the total costs. From an economic point of view, treatments should as much as possible be administered on an outpatient basis, of course depending on the condition of the patient.

The policy impact of Chapters 4 and 5 is clear: given the faster haematological recovery, faster discharge from hospital, lower costs and a higher quality-of-life, the rescue therapy after high-dose second-line chemotherapy for younger patients should be peripheral blood stem cell transplantation (PBSCT) instead of autologous bone marrow transplantation (ABMT). From the late 1990's onwards, PBSCT had already become the standard rescue therapy, and in this sense, the results of the studies in Chapters 4 and 5 have primarily been a justification of this shift from PBSCT to ABMT. Notwithstanding the results, the study (known in the Netherlands as the HOVON-22 study) indicated that new approaches are warranted to further improve the results in this patient group. Following this conclusion, the HOVON-22 has been the predecessor for the current HOVON-44 study, in which a similar regimen is applied to which the monoclonal antibody rituximab has been added, which might be one of these promising new steps for patients with relapsed or refractory aggressive NHL.
Chapter 9 showed the ability to use the International Prognostic Index for Aggressive NHL (IPI) for the distinction of subgroups of patients according to their cost profiles, beyond its traditional use. Also, the variable 'B-symptoms' was a significant cost determinant. This is an important finding, as new pharmaceuticals are marketed for NHL, which are often relatively expensive. Therefore, it might be beneficial if subgroups can be determined at forehand in which the largest cost-effectiveness gains might be expected. It turned out that high costs within unfavourable cost profiles were mainly caused by hospitalisation costs. Therefore, new pharmaceuticals that are successful in reducing complications and related hospitalisations might induce high cost-effectiveness gains. This is a finding that can easily be used in daily practice, as all IPI factors and the presence of B-symptoms are already scored at initial diagnosis, and it does therefore not call upon additional data collection.

Recommendations for future studies and use of published data

In Chapter 3, it was recommended to base health care economic evaluations as much as possible on data from different hospitals, in order to eliminate the influence of hospital specific policies. This recommendation applies to both the resource use of patients as well as to the unit costs that are applied to the resource use items. Average unit costs should be based on financial data from several hospitals and these should be applied to the resource use of all patients in the study, instead of applying specific unit costs for each hospital in the study.
For those who perform economic modelling studies in aggressive NHL, Chapter 6 of this thesis may serve as a useful data source. Beyond the presentation of detailed data on studies performed before, this literature review showed the ranges in which outcome measures like overall survival or complete response may vary. These data may be used as a basis for sensitivity analyses within this kind of studies, they allow for testing the influence of changing assumptions about survival or response on the cost-effectiveness ratio of treatments.

For authors of clinical trials, Chapter 6 demonstrated the urgent need for highly detailed presentations of exclusion criteria, patient characteristics and outcomes if the publications of their trials are to be used for improving patient care or making health policy decisions. Many older publications suffered from the lack of a sufficient level of detail, which importantly diminishes their usefulness. For example, generalisation from published data can only be done after careful scrutiny of the patient characteristics among different groups.

The literature review on all economic evaluations on NHL (Chapter 10) was primarily performed to help oncologists and haematologists in judging the value of these studies, as the different methodologies and assumptions in the available publications often make them incomparable. However, for those who perform economic evaluations in NHL, it also stressed the importance of making adequate methodological choices. Six methodological issues that are important in economic evaluations were mentioned: the study perspective should have been reported clearly, overhead costs should have been included appropriately, appropriate sources (financial administrations of hospitals) should have been used for the calculation of unit costs, unit costs should have been based on real prices instead of charges, a sensitivity analysis should have been performed, and separate presentations of resource use and costs should have been included. Particularly the latter aspect is important, as this allows readers to redo calculations on the basis of their own assumptions. It should at least be mentioned in the publications how these methodological issues were tackled, even if they were not tackled in the recommended way. However, a need for more standardisation of economic evaluations in NHL becomes clear from this review and the recommendations in this review may possibly contribute to this. The review also indicated the topics that remain to be appropriately studied in economic evaluations of NHL: standard therapies, oral fludarabine, and allogeneic / autologous stem cell transplantation for indolent NHL, and monoclonal antibodies (rituximab and alemtuzumab) for indolent and aggressive NHL.

Recommendations for medical practice

Chapter 6 demonstrated the need for strictly applying response criteria (on which consensus has already been reached[2]) and the WHO histology classification system. This is expected to lead to ameliorated possibilities to compare results from different clinical trials, as earlier response criteria allowed for subjectivity, and former histology classification systems have been shown to 'suffer' from heterogeneity within subclasses. Stratification of patients on the basis of prognostic factors (like those from the IPI system) is also expected to lead to a better comparability (and therefore to a better generalisability) of trial results.

To obtain 'daily practice results' that are comparable to results obtained in randomised clinical trials, the importance of strict protocol adherence was stressed, with regard to diagnostic (for initial staging and restaging) and therapeutic modalities. The positive message from this statement is that patient

survival may be better when patients are treated according to standard protocols and that protocol-defined treatment schedules have been supposed to lead to better results[3, 4].
Although it is not a novelty, Chapter 7 showed that patient survival is significantly better in case a complete remission is reached with the first-line treatment. Therefore, haematologists should as much as possible try to induce complete remissions in these patients, and strict protocol adherence might certainly contribute to this.

Recommendations for trial participation

Above, it was concluded that strict protocol adherence might lead to better results. The best guarantee for strict protocol adherence is certainly to include patients in a clinical trial.
On theoretical grounds, Chapters 6 and 7 discussed that RCT results obtained in younger patients can be generalisable, whereas in elderly patients such generalisability is often not obvious. Elderly patients often suffer from co-morbidity, which might exclude them from clinical trials. Furthermore, in case of complications, chemotherapy in elderly patients is often stopped relatively soon. The survey (Chapter 2) had shown that there still remains something to be gained in this situation. Moreover, the analyses in Chapters 7 and 8 had shown that comparable results among RCT and SLP patients can be obtained, even if patients with co-morbidity are included in the SLP groups. Therefore, if a patient's co-morbidity allows the administration of optimal therapy for NHL, he or she can very well be invited for trial participation, within the limits set by the exclusion criteria. This will also enhance the representativeness of the trial results for SLP. Furthermore, the discussion of Chapter 8 indicated that despite our results, a comparison with other RCTs in elderly patients might have led to the conclusion that RCTs in elderly patients lead to better results than SLP.
On the basis of empirical data, this thesis comprised the finding that RCTs in aggressive NHL can be representative for SLP. As the primary aim of all RCTs is to ensure a high internal validity, the proper external validity in aggressive NHL should be considered as a positive side effect, and an additional argument for including aggressive NHL patients in clinical trials.
Including patients in clinical trials is needed for continuous progress in medicine. The literature review in Chapter 6 stressed the importance of including sufficient patient numbers in clinical trials and to perform multicentre trials as much as possible. The most divergent results in this literature review were obtained from single centre trials or from trials that had included less than 100 patients. Furthermore, an argument for intergroup trials can be pushed forward on the basis of these statements. As the latest developments in NHL are moving quite fast as compared to the previous 25 years, trials are particularly useful when they provide answers to clinically relevant questions as soon as possible. In haemato-oncology, several trial groups are active within Europe and the United States, which enables the possibility to join forces in order to move forward quickly, on behalf of improved patient outcomes.

But what about the somewhat higher costs in elderly RCT patients, as concluded in Chapter 8? It appears reasonable to conclude that these are justified and a positive finding is that these may even be reduced (see below). From the analysis in Chapter 8, it became clear that in SLP less diagnostics are performed. In particular, too less radiological tests are done, which corresponds to findings of the earlier survey (Chapter 2). The RCT recommendations for radiological diagnostics are not very different from 'best practice recommendations', and they are similar to the recommendations in the new national guideline for NHL. Therefore, instead of concluding that these costs were higher in RCT settings, one might also conclude that the costs in the SLP settings are too low to ensure optimal quality of care. Moreover, the finding that more diagnostic tests were performed in the protocolled trial settings is an important one, because they were performed at 'clinical decision making moments', i.e. whether or not to continue the ongoing treatment or to switch to alternative chemotherapy. By avoiding unnecessary and ineffective treatment in non-responding patients, this might justify somewhat higher costs in elderly patients. Also, the strictly protocolled treatments might prevent misunderstandings with regard to the required diagnostic procedures. It is sometimes suggested that in SLP, diagnostic tests might be left undone if they do not alter treatment decisions, but this is actually a misconception. If for example a bone-marrow biopsy is not performed because the patient is already known to have a stage IV NHL (and the procedure is considered to be unpleasant for the patient), one is not able to adequately assess the effect of chemotherapy. The ignorance about a bone-marrow localisation might lead to the erroneous conclusion that the patient has reached a complete remission, with the possibly fatal implication of not administering a second-line treatment or consolidation radiotherapy.

The 'other reason' why the costs in elderly RCT patients were somewhat higher was hospitalisation. The main type of hospital days that was occurring more frequently in elderly RCT patients was 'hospitalisation for therapy'. The number of hospital days for complications was approximately the same among the SLP and RCT groups. This implies that the costs of elderly RCT patients can probably be reduced somewhat, as therapy might also very well be administered on an outpatient basis. It may have been possible that the doctor's knowledge of having a patient included in a clinical trial might induce the doctor more easily to hospitalise the patient for therapy, while this is not strictly necessary if no complications are expected at forehand.

All in all, an argument was made for treating patients in clinical trials as much as possible. Particularly nowadays, this argument appears to be valid, as recent developments in NHL are encouraging and trial participation should therefore be stimulated.

In considering this statement, it should be kept in mind that the comparisons in this thesis were based on groups of patients who all received treatment. However, this was done on purpose, as the inclusion of not-treated or only palliatively-treated patients in the SLP groups would at forehand have led to the conclusion of superiority of RCT treatment over SLP treatment. Also the conclusions all relate to phase III clinical trials, in which the current standard treatment is compared to a possibly superior alternative of which the safety, safe doses, and side effects have already been determined in earlier phase studies. The conclusions also assume that additional costs caused by the new intervention

under study are borne by for example the pharmaceutical company that has an interest in the study. In case the new treatment is both superior and more expensive as compared to the current standard treatment, the question whether the new treatment should be considered for reimbursement after completion of the trial is detached from the findings in this thesis, because this has more to do with internal validity (the relative superiority of the new treatment over the current one) than with external validity (the representativeness of the absolute results for daily practice).

The RCT versus SLP question in the light of Tugwell's framework

A framework for comparing RCT to SLP was presented in the introductory chapter of this thesis. Five types of bottlenecks in the care process that might be responsible for differences between efficacy and effectiveness were recognised[5], on the basis of a model by Tugwell and colleagues[6]. In the light of the findings of this thesis, it will be discussed below to what extent these five bottlenecks might be responsible for difference between efficacy and effectiveness in the area of aggressive NHL.

First bottleneck: the time the patient contacts a health care professional. If the patient waits relatively long with contacting a health care professional, the disease might have developed to a more advanced stage, which might negatively impact the results of treatment. In the case of NHL, the occurrence of such a patient delay is possible, as symptoms may be relatively vague and minor during several months before they lead to obvious complaints, like a swollen lymph node or pain[7]. However, the decision to treat a patient in an RCT is only made when the diagnostic process has been completed, and therefore, in aggressive NHL, this patient delay will not cause any differences between outcomes of RCT and SLP treatment. This argument is also true for RCTs in aggressive NHL that have been performed in the past and therefore, this bottleneck does not play any role in explaining differences between efficacy and effectiveness in this area.

Second bottleneck: adequate (and timely) diagnosis of the patient's disease. Effectiveness may be worse than efficacy if the diagnosis is not made, not adequately or when it is made too late. Such a delay caused by the doctor may occur when for example the general practitioner does not (timely) recognise the patient's complaints as an indication of NHL. In NHL, this is not impossible, as at initial diagnosis, about one third of the patients suffer from general complaints, like fever, night sweating, tiredness or weight loss[7]. However, with regard to this observation, the same is supposed to be true as for the first bottleneck: this probably does not contribute to a difference between RCT and SLP. Nevertheless, once patient complaints have been recognised as indications of NHL, differences between efficacy and effectiveness might occur on this subject. As became clear from this thesis, the chance of applying all required diagnostic modalities is certainly increased once it has been suggested to offer the patient an RCT treatment. In this context, the example of the bone marrow biopsy and its possibly negative therapy implication has been mentioned above in this General Discussion.

Third bottleneck: indications for a health care intervention (the extent to which patients receive efficacious health care interventions). The standard first-line therapy for aggressive NHL has been the same for almost three decades. With regard to second-line therapy, the place of the standard therapy for younger patients has also been established during the past decade. It is therefore supposed to be rather implausible that NHL patients do not receive receive the recommended therapy. If aggressive NHL patients do not receive recommended treatments, this is only after careful consideration with the patient. In one of the chapters of this thesis, it was shown that 10 out of 79 newly diagnosed patients did not undergo treatment, and good reasons for this decision were present in all of them. The chance that aggressive NHL patients will receive recommended treatments is assumed to increase even further in the near future, due to the national guidelines for NHL that will be published in 2004.

Fourth bottleneck: adequate realisation of the health care intervention. A difference between efficacy and effectiveness may also occur if recommended treatments are not administered optimally. In this thesis, it was shown that this also occurs with regard to aggressive NHL. In elderly SLP patients, doses of chemotherapy were reduced somewhat more frequently or chemotherapy cycles were delayed more often in case of complications, while this is discouraged because of a negative impact on treatment results. The occurrence of inadequate dose reduction or delay of cycles might possibly also be reduced further as a consequence of the new national guidelines for NHL.

Fifth bottleneck: compliance of the patient with the therapy. In contrast to many other diseases, this bottleneck is assumed not to be responsible for differences between efficacy and effectiveness that might occur in the area of aggressive NHL. The therapies for aggressive NHL are all scheduled by the haematologist and do not require long-term home-use of any drugs. In this disease, doctor's compliance is assumed to be far more important than patient compliance.

According to this framework of Tugwell and colleagues, a difference between efficacy and effectiveness in the area of aggressive NHL is mainly assumed to be caused by the second and fourth bottleneck. However, in this thesis it was shown that RCT results in aggressive NHL can be representative for SLP results, and the introduction of national guidelines may be supposed to even positively contribute to this situation. Therefore, this probability for generalisation is assumed to be also valid in the near future.

Final remarks

This thesis focused on economic evaluations in aggressive NHL, and primarily focused on the actual cost level of treatments. However, it has to be kept in mind that a reliable estimation of these costs could only be made after thorough inventory and careful scrutiny of all diagnostic and therapeutic modalities applied for these patients. In this respect, the data showed that a trial treatment simply guarantees the application of timely, adequate and optimal diagnostic and therapeutic modalities.

It should be noticed that the conclusions drawn in this thesis with regard to generalisability of RCT results do not automatically apply to other diseases. As already mentioned in Chapter 8, the conclusions may not be valid if a major part of the patient group is not eligible for trial inclusion due to selective eligibility criteria, or in the case non-eligible patients suffer from characteristics that prevent them from being included in an RCT or that markedly distinguish them from RCT patients (e.g. poorer performance status). This also applies to diseases for which more than one standard treatment exists and no consensus has been reached about the treatment of first choice. Also, the conclusions will probably be different for treatments that are highly dependent on patient compliance, because the treatments considered in this thesis are actually more dependent on doctor's compliance (performing adequate diagnostic and therapeutic procedures on pre-scheduled times) than on patient compliance.
Both literature reviews within this thesis showed the importance of reporting results in detail, if they were written to be used by others. Both also underlined the need for standardisation in NHL studies: with respect to more uniformity among costing studies on the one hand and with respect to the application of internationally agreed response criteria and the WHO histology classification system on the other hand.

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Summary

Non-Hodgkin's lymphoma (NHL) is the most prevalent of all haematological malignancies. The group of NHL consists of a variety of subtypes, but the majority of NHL patients suffer from so-called 'aggressive' NHL. Most of the aggressive NHL patients have disseminated disease (stage II-IV). For stage II-IV aggressive NHL, the standard first-line therapy has been 6-8 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy ever since 1976. In case of refractory or recurrent NHL in younger patients who have shown to be sensitive to chemotherapy, high-dose chemotherapy followed by stem cell transplantation is the treatment of choice. For elderly patients, and for younger patients who have not shown sensitivity to chemotherapy, no standard second-line treatment exists. Many NHL patients are offered treatment in a randomised clinical trial (RCT). NHL is among the small number of malignancies that have shown markedly increased incidence and mortality rates during the recent past. In the same time, health care costs in developed countries have risen faster than the general inflation rate. Given these figures, this thesis focuses on economics of diagnosis, treatment and follow-up in stage II-IV aggressive NHL.

In Chapter 2, an overview of the current situation with regard to management of aggressive NHL patients (diagnosis, treatment, and follow-up) was presented, based on an analysis on current treatment guidelines and a survey among haematologists. This overview confirmed the agreement on the first-line treatment. No agreement existed on second-line treatments (except for high-dose chemotherapy followed by stem cell transplantation in younger patients). It was shown that in daily clinical practice, diagnostic tests were sometimes left undone, and that chemotherapy was stopped or reduced sooner in the case of thrombocytopenia or leukocytopenia. Many of the surveyed haematologists said to include patients with aggressive NHL in RCTs, although the actual participation rate appears to be rather low, an inconsistency that might be due to the selection of surveyed haematologists. Factors hindering trial participation were lack of time, logistic problems, and the ethics committee procedure.

Chapter 3 presented the costs of the initial diagnostic phase, costs of the standard CHOP and CHVmP/BV (cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine) first-line treatments, and costs of one year disease-free follow-up. Furthermore, this study yielded some first insights into cost difference between RCTs and treatment according to 'standard local practice' (SLP). Costs were within comparable ranges, although costs of diagnostics appeared to be somewhat higher within the RCT settings. CHVmP/BV chemotherapy was more expensive than CHOP, because of an additional infusion of cytostatics at mid-cycle.

Consequently, Chapters 4 and 5 were focused on the standard second-line chemotherapy for younger chemotherapy-sensitive patients with refractory or recurrent aggressive NHL. In an RCT (Chapter 4), peripheral blood stem cell transplantation (PBSCT) was shown to be superior to autologous bone marrow transplantation (ABMT) as rescue therapy after high-dose chemotherapy. PBSCT patients showed a faster engraftment of neutrophils and thrombocytes, and they required fewer transfusions of

red blood cells and platelets. The number of days with fever and the number of days with intravenous antibiotics in patients with fever were significantly lower in the PBSCT group. Furthermore, PBSCT patients had lower costs and a better quality of life than ABMT patients (Chapter 5). The quality of life of this patient group finally turned out to be comparable to the quality of life of other cancer patients.

A literature review in Chapter 6 emphasised that not all the results obtained with standard CHOP in RCTs during the past 25 years are comparable to each other. Differences within the outcome measures could not unanimously be explained by differences in patient and treatment characteristics. Therefore, not all RCT results are representative of results obtained in SLP, and generalisation of the absolute trial result should only be done after careful scrutiny of patient-, disease-, and study characteristics. In this respect, age of the patients, histology of the NHL, and sample sizes of the studies were most important.

Chapter 7 comprised a single-centre study, which showed that the survival of patients with aggressive NHL did not differ by treatment (RCT or SLP) during the years 1994-2001. In this centre, SLP and RCT patients received equally effective therapy. RCT inclusion was recommended because of strict patient monitoring and promising future developments. Together with the comparable cost data within RCT and SLP settings (Chapter 3), this study led to a study on both costs and effects in larger patient groups.

In this larger study, presented in Chapter 8, costs and survival were concluded to be comparable between younger RCT and SLP patients. This implies that RCT costs and effects in younger aggressive NHL patients can be representative of SLP costs and effects. In elderly patients, survival was also identical, but the costs of the first-line treatment were 11 to 13% higher in the case of RCT treatment. However, these somewhat higher costs might be justified, because of the conclusion that diagnostic tests are applied more properly in the RCT setting, which may have crucial implications for these patients. As some doubts were raised about our elderly patients RCT group, it might in the end be possible that in elderly patients, RCTs will generally result in a somewhat higher survival compared to SLP, without contributing to importantly higher costs.

The consequent study in Chapter 9 presented costs of all parts of the disease course in detail. This study confirmed that there is no agreement on second-line treatments and that the costs occurring after the first-line treatment are highly dependent on a relatively small number of patients and on the types of treatments applied in these patients. Costs of second-line treatments appeared to be highly variable. The study focused on factors influencing treatment costs and it was shown that the International Prognostic Index for Aggressive NHL, which has been used for years to predict survival, is also very predictive of total treatment costs. Also, the presence of B-symptoms (fever, night sweats, weight loss) turned out to be a very significant cost determinant.

In Chapter 10, the current state of affairs with regard to economic evaluations in NHL was presented. This literature review grouped all available publications according to the different topics that have been studied in NHL economic evaluations and it valued these evaluations no the basis of their methodological merits. Topics studied in NHL economic evaluations were: standard first-line therapy

for aggressive NHL, haematopoietic growth factors accompanying first-line chemotherapy for aggressive NHL, and high-dose first-line therapy for aggressive NHL. With regard to second-line therapy for aggressive NHL, the following topics have been subjected to economic evaluations: high-dose chemotherapy (HDC) with stem cell transplantation (SCT), ABMT versus PBSCT, learning effects of HDC + SCT, haematopoietic growth factors following SCT, CD34+ dose in the SCT procedure. For indolent NHL, costs of standard chemotherapy have been calculated. Finally, studies were performed on trial costs, and rasburicase for hyperuricaemia. Methodological points that should be awarded and addressed properly in (NHL) economic evaluations are: appropriate study perspective, appropriate inclusion of overhead costs, basing unit costs preferably on data from the hospital's financial departments, basing unit costs preferably on real prices (instead of charges), performing sensitivity analyses, and separate presentations of both resource use and unit costs.

Samenvatting

Non-Hodgkin lymfoom (NHL) is de meestvoorkomende hematologische kanker. NHL is in feite een benaming voor een verzameling van lymfatische maligniteiten; de meerderheid van de NHL-patiënten lijdt aan het zogenaamde 'agressieve' NHL. De meeste patiënten met agressief NHL hebben gedissemineerde ziekte (stadium II-IV). De standaard eerstelijns-behandeling voor stadium II-IV agressief NHL is CHOP (cyclofosfamide, doxorubicine, vincristine, prednison) chemotherapie, reeds sinds 1976. In geval van recidief of refractair NHL bij jongere patiënten die gevoelig zijn gebleken voor chemotherapie, dan is hoge-dosischemotherapie gevolgd door stamceltransplantatie de behandeling van eerste keus. Voor oudere patiënten, en voor jongere patiënten die niet gevoelig bleken voor chemotherapie is er geen standaard tweedelijns-behandeling. Aan veel NHL-patiënten wordt de mogelijkheid voor behandeling in een gerandomiseerd klinisch onderzoek (RCT) geboden. NHL is een van de weinige maligniteiten met een opmerkelijke toename in incidentie en mortaliteit in het recente verleden. Gedurende dezelfde tijd zijn de gezondheidszorgkosten in ontwikkelde landen sneller gestegen dan de algehele inflatie. Gegeven deze ontwikkelingen is dit proefschrift gericht op economische evaluaties van diagnostiek, behandeling en follow-up van patiënten met stadium II-IV agressief NHL.

In hoofdstuk 2 werd een overzicht gegeven van de huidige situatie met betrekking tot diagnostiek, behandeling en follow-up van patiënten met een agressief NHL, op basis van een analyse van huidige behandelingsrichtlijnen en een enquête onder hematologen. Dit overzicht bevestigde de eensgezindheid ten aanzien van de eerstelijns-behandeling. Er bestond geen eensgezindheid over tweedelijns-behandelingen (behalve over hoge-dosis chemotherapie gevolgd door stamceltransplantatie voor jongere patiënten). In de dagelijkse klinische praktijk bleken sommige diagnostische tests wel eens achterwege gelaten te worden. Tevens werd in de dagelijkse praktijk chemotherapie sneller gestaakt of werd sneller overgegaan tot dosisreductie in geval van thrombocytopenie of leukocytopenie. Veel van de geënquêteerde hematologen zeiden patiënten met agressief NHL in RCTs te includeren, hoewel de daadwerkelijke participatie nogal laag lijkt. Deze inconsistentie kan te wijten zijn aan de selectie van geënquêteerde hematologen. Factoren die trialparticipatie belemmeren, waren een gebrek aan tijd, logistieke problemen en de procedure rond de medisch-ethische commissie.

Hoofdstuk 3 presenteerde de kosten van de initiële diagnostische fase, kosten van de standaard CHOP en CHVmP/BV (cyclofosfamide, doxorubicine, teniposide, prednison, bleomycine, vincristine) eerstelijns-behandelingen, en kosten van één jaar ziektevrije follow-up. Voorts leverde deze studie de eerste inzichten op met betrekking tot verschillen in kosten tussen RCTs en behandelingen volgens de 'standaard lokale praktijk' (SLP). De kosten waren in vergelijkbare orde van grootte, hoewel de kosten van diagnostiek iets hoger waren in de RCTs. CHVmP/BV chemotherapie was duurder dan CHOP, vanwege een extra cytostaticatoediening halverwege elke kuur.

Vervolgens waren de hoofdstukken 4 en 5 gericht op de standaard tweedelijns-behandeling voor jongere chemotherapie-gevoelige patiënten met refractair of recidief agressief NHL. In een RCT (Hoofdstuk 4) werd aangetoond dat perifere-bloedstamceltransplantatie (PBSCT) superieur was aan autologe beenmergtransplantatie (ABMT) als ondersteunende therapie na hoge-dosischemotherapie. PBSCT-patiënten toonden een sneller herstel van neutrofielen en thrombocyten en zij hadden minder transfusies nodig van rode bloedcellen en bloedplaatjes dan ABMT-patiënten. Het aantal dagen met koorts en het aantal dagen met koorts waarop intraveneuze antibiotica werden toegediend, waren significant lager in de PBSCT-groep. Verder hadden de PBSCT-patiënten lagere kosten en een betere kwaliteit van leven dan ABMT-patiënten (Hoofdstuk 5). Tenslotte bleek de kwaliteit van leven van deze patiëntengroep goed vergelijkbaar te zijn met die van andere kankerpatiënten.
Een literatuuronderzoek in hoofdstuk 6 benadrukte dat niet alle resultaten behaald met standaard CHOP in RCTs gedurende de afgelopen 25 jaar vergelijkbaar zijn met elkaar. De verschillen in de uitkomstmaten konden niet unaniem verklaard worden door verschillen in patiënten- en behandelingskenmerken. Daarom zijn niet alle RCT-resultaten representatief voor SLP-resultaten. Generaliseren van het absolute trialresultaat kan daarom slechts geschieden na een zorgvuldig onderzoek van de patiënt-, ziekte- en studiekenmerken. In dit opzicht waren leeftijd van de patiënt, histologie van het NHL en steekproefgrootte van de studie de belangrijkste factoren.
Hoofdstuk 7 bevatte een studie uitgevoerd in één ziekenhuis, die aantoonde dat de overleving van patiënten met agressief NHL niet verschilde tussen RCT en SLP gedurende de jaren 1994-2001. In dit ziekenhuis ondergingen RCT- en SLP-patiënten therapie van gelijke effectiviteit. RCT-inclusie werd aanbevolen vanwege de strikte monitoring van patiënten en veelbelovende toekomstige ontwikkelingen. Tezamen met de vergelijkbare kosten in RCT en SLP (Hoofdstuk 3) was deze studie de aanzet voor een studie naar zowel kosten als effecten op basis van grotere patiëntengroepen.
In deze grotere studie, gepresenteerd in hoofdstuk 8, werd geconcludeerd dat kosten en overleving vergelijkbaar waren tussen jongere RCT- en SLP-patiënten. Dit impliceert dat kosten en effecten uit RCTs bij jongere patiënten met agressief NHL representatief kunnen zijn voor kosten en effecten in SLP. Bij de oudere patiënten was de overleving eveneens identiek, maar de kosten waren 11 tot 13% hoger in geval van RCT. Echter, deze iets hogere kosten lijken gerechtvaardigd, vanwege de conclusie dat diagnostiek adequater wordt uitgevoerd in RCTs, wat cruciale implicaties voor deze patiënten kan hebben. Daar er enige twijfel was gerezen over de oudere RCT-patiëntengroep, zou het uiteindelijk mogelijk kunnen zijn dat RCTs bij oudere patiënten resulteren in een iets betere overleving dan SLP, zonder daarbij te leiden tot belangrijk hogere kosten.
De studie in hoofdstuk 9 presenteerde de kosten van alle delen van het ziekteverloop in detail. Deze studie bevestigde dat er geen overeenstemming heerst over tweedelijns-behandelingen en dat de kosten die na de eerstelijns-behandeling optreden sterk afhankelijk zijn van een relatief klein aantal patiënten en van het type behandeling voor deze patiënten. De kosten van tweedelijns-behandelingen vertoonden zeer veel variatie. De studie was gericht op factoren die behandelingskosten beïnvloeden en toonde aan dat de International Prognostic Index for Aggressive NHL, die reeds lange tijd wordt

gebruikt voor het voorspellen van overleving, ook een voorspellende waarde heeft voor de totale behandelingskosten. Tevens was de aanwezigheid van B-symptomen (koorts, nachtzweten, gewichtsverlies) een belangrijke determinant van de kosten.

In hoofdstuk 10 werd de huidige stand van zaken met betrekking tot economische evaluaties bij NHL weergegeven. Dit literatuuronderzoek groepeerde alle beschikbare publicaties op grond van de verschillende onderwerpen die in economische evaluaties bij NHL geanalyseerd werden. Tevens werden deze publicaties beoordeeld op grond van hun methodologische kenmerken. Onderwerpen die in economische evaluaties bij NHL geanalyseerd werden, waren: standaard eerstelijns-behandeling voor agressief NHL, hematopoietische groeifactoren bij eerstelijns-chemotherapie voor agressief NHL, hoge-dosis eerstelijns-therapie voor agressief NHL. Met betrekking tot de tweedelijns-behandeling voor agressief NHL werden de volgende onderwerpen in economische evaluaties beschouwd: hoge-dosis chemotherapie (HDC) met stamceltransplantatie (SCT), ABMT versus PBSCT, leereffecten van HDC+SCT, hematopoietische groeifactoren na SCT, CD34+ dosis bij SCT. Voor indolent NHL werden kosten van standaard chemotherapie berekend. Tenslotte werden studies uitgevoerd naar trialkosten en rasburicase voor hyperuricaemie. Methodologische onderwerpen die adequaat behandeld zouden moeten worden in economische evaluaties (bij NHL) zijn: een geschikt studieperspectief, een adequate toerekening van overheadkosten, het bij voorkeur baseren van kostprijzen op gegevens van financiële administraties van de ziekenhuizen, het bij voorkeur baseren van kostprijzen op daadwerkelijke prijzen (in plaats van tarieven), het uitvoeren van gevoeligheidsanalyses, en een aparte presentatie van zorgconsumptie en kostprijzen.

List of abbreviations

2YS	two-year overall survival
ABMT	autologous bone marrow transplantation
ACVBP	chemotherapy consisting of doxorubicine, cyclophosphamide, vindesine, bleomycin, methylprednisone
AIDS	acquired immunodeficiency syndrome
BEAC	chemotherapy consisting of carmustine, etoposide, cytarabine, cyclophosphamide
BEAM	chemotherapy consisting of carmustine, etoposide, cytarabine, melphalan
CEP	chemotherapy consisting of chlorambucil, etoposide, prednisone
CHOP	chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, prednisone
CHvMP/BV	chemotherapy consisting of cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine
CI	confidence interval
COP	chemotherapy regimen consisting of cyclophosphamide, vincristine, prednisone
COPD	chronic obstructive pulmonary disease
CR	complete response
CT	computed tomography
CVP	chemotherapy regimen consisting of cyclophosphamide, vincristine, prednisone
DHAP	chemotherapy consisting of dexamethasone, cytarabine, cisplatin
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EE	economic evaluation
EFS	event-free survival
ELD	elderly patients
EORTC	European Organization for Research and Treatment of Cancer
EORTC-20901	RCT comparing standard 8x CHvMP/BV with 6x standard CHvMP/BV + ABMT
EORTC-20932	RCT comparing CHvMP/BV with CHvMP/BV + RT
EQ vas	EuroQol visual analogue scale
EQ-5D index	EuroQol 5 dimension index
FACS	fluorescence-activated cell sorter
G-CSF	granulocyte colony-stimulating factor
GM-CFU	granulocyte-macrophage colony-forming units
GM-CSF	granulocyte-macrophage colony-stimulating factor
Gy	Gray
Hb	haemoglobin

HD	Hodgkin's disease
HDC	high-dose chemotherapy
HGF	haematopoietic growth factor
HIV	human immunodeficiency virus
HOVON	Dutch Working Group on Adult Haemato-Oncology
HOVON-22	RCT comparing ABMT with PBSCT as rescue therapy following DHAP-VIM-DHAP+BEAM chemotherapy
HOVON-25	RCT comparing standard 3-weekly CHOP with standard 3-weekly CHOP+G-CSF
HOVON-26	RCT comparing standard 3-weekly CHOP with intensified 2-weekly CHOP+G-CSF
HOVON-44	RCT comparing DHAP-VIM-DHAP followed by BEAM + PBSCT with the same regimen to which rituximab is added to the DHAP-VIM-DHAP scheme
IF	involved field
IMVP	chemotherapy consisting of ifosfamide, mesna, etoposide, methotrexate
IPI	International Prognostic Index for aggressive non-Hodgkin's lymphoma
IQR	interquartile range
iv	intravenously
LDH	lactate dehydrogenase
MACOP-B	chemotherapy consisting of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin
MH	morbus Hodgkin
MPA	matched pairs analysis
NCVBP	chemotherapy consisting of mitoxantrone, cyclophosphamide, vindesine, bleomycin, methylprednisone
NHL	non-Hodgkin's lymphoma
ns	not significant
OR	overall response
OS	overall survival
P(B)SCT	peripheral (blood) stem cell transplantation
PLT	platelet
PR	partial response
ProMACE-CytaBOM	chemotherapy consisting of cyclophosphamide, etoposide, prednisone, cytarabine, vincristine, bleomycin, methotrexate, leucovorin
ProMACE-MOPP	chemotherapy consisting of prednisone, methotrexate, leucovorin, doxorubicin, cyclophosphamide, etoposide, mitoxine, vincristine, procarbazine
PROT	protocol treatment
QoL	quality of life

RBC	red blood cell
RCC	Regional Cancer Centre
R-CHOP	CHOP + rituximab
RCP	routine clinical practice
RCT	randomised clinical trial
REAL	Revised European-American Lymphoma classification
rG-CSF	recombinant human granulocyte colony-stimulating factor
RSCL	Rotterdam Symptom Checklist quality of life measurement
RSCL ALI	RSCL activity level impairment
RSCL PDL	RSCL psychological distress level
RSCL PSDL	RSCL physical symptom distress level
RSCL-i	RSCL item score
RT	radiotherapy
SCT	stem cell transplantation
SD	standard deviation
SF-36	Short Form 36 quality of life measurement
SF-36 BP	SF-36 bodily pain
SF-36 GH	SF-36 general health
SF-36 MCS	SF-36 mental composite score
SF-36 MH	SF-36 mental health
SF-36 PCS	SF-36 physical composite score
SF-36 PF	SF-36 physical functioning
SF-36 RE	SF-36 role functioning-emotional
SF-36 RP	SF-36 role functioning-physical
SF-36 SF	SF-36 social functioning
SF-36 VT	SF-36 vitality
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SLP	standard local practice
SPSS	Statistical Package for the Social Sciences
ULN	upper limit of normal level
VIM	chemotherapy consisting of etoposide, ifosfamide, mesna, methotrexate
VWS	Dutch Ministry of Public Health, Welfare and Sport
WBC	white blood cell
WF	Working Formulation
WHO	World Health Organization
YNG	younger patients

Curriculum vitae

Michel van Agthoven was born in Alkmaar on October 28, 1975. After having followed secondary school in Rotterdam, he studied Health Care Policy and Management at the Erasmus University Rotterdam from 1994 to 1998. He graduated on the basis of a study on the costs of liver transplantation (a project in cooperation with the Departments of Surgery and Internal Medicine of the Erasmus MC, University Medical Centre Rotterdam). From June 1998 onwards, he has been working at the Institute for Medical Technology Assessment / Department of Health Care Policy and Management at the Erasmus MC, University Medical Centre Rotterdam. His research activities are focused on economic evaluations of cancer treatments, particularly with regard to haematological malignancies and head-and-neck oncology. During the years 2001-2004, he was one of the organising members of the national working group that was responsible for the development of clinical practice guidelines for non-Hodgkin's lymphoma.

Nawoord

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