Cost determinants in aggressive non-Hodgkin's lymphoma

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The 5 factors of the International Prognostic Index (IPI) for aggressive non Hodgkin's lymphoma (NHL) age, disease stage, serum lactate dehydrogenase (LDH), performance status, number of extranodal sites) are validated predictors of a patient's survival. Given the need for economic evaluations, we analyzed whether the IPI and the presence of B-symptoms (night sweats, fever, weight loss) can identify subgroups of patients with favorable or unfavorable cost profiles. Chart data for 374 patients with newly diagnosed stage II-IV aggressive NHL treated between 1993-2001 with CHOP chemotherapy were used. Costs were calculated up to two years from the start of treatment. The cost of granulocyte colony-stimulating factor (G-CSF) was not included, as some patients received this due to trial participation. Regression analyses and non-parametric bootstrap tests were performed to determine the significance of prognostic factors. Mean first-line treatment costs (excluding G-CSF) were €10047 (<60 years) and €12232 (>60 years). Two-year follow-up costs averaged €14039 and €9026 for the two age groups, respectively. The 5 IPI variables, the 2 IPI risk group variables (resulting from the 5 factors) and B-symptoms all showed significant univariate associations with first-line treatment costs. They were also associated with higher 2-year costs, except for age, LDH, and standard risk group index. Lower predictability of total 2-year costs was due to wide variations in second-line treatments. The IPI factors and B-symptoms are predictive of treatment costs. The detailed information presented in this paper is of value for those who need to make cost-effectiveness estimations in NHL, which is a relevant topic, given new treatment modalities that are emerging.

Key words: non-Hodgkin's lymphoma, diffuse large-cell lymphoma, cost and cost analysis, economics, antineoplastic combined chemotherapy protocols

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Of all hematologic malignancies, non-Hodgkin's lymphoma (NHL) has the highest incidence rate.[1] In the USA, the number of deaths attributable to NHL ranks among the top five cancer-related deaths, and NHL is among the small number of malignancies that have shown markedly increased incidences and mortality rates during the past decade.[2,3] The standard first-line treatment for the most prevalent type of NHL (aggressive NHL) has been CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy since 1976.[4-6] Only recently has research on the treatment of NHL 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 patients with diffuse large B-cell lymphoma. In aggressive NHL, rituximab is an addition to CHOP therapy and not a replacement of standard therapy. Such developments have major financial consequences, as new pharmaceuticals are usually relatively expensive. Therefore, in some countries, pharmaceutical companies are (or will soon 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 the limited health care resources, and the high costs of new pharmaceuticals, which may be more efficacious than the current standard therapy. Therefore, it might be helpful if subgroups of patients can be identified in whom new drugs are expected to lead to improvements in the cost-effectiveness ratio, given the costs and effects obtained in these patients with current therapies. In 1993, a system was validated that can be used to distinguish groups of patients with aggressive NHL who receive doxoru-

bicin-containing combination chemotherapy according to their different survival patterns. In this *International Prognostic Index* (IPI) for aggressive NHL, patients are categorized into several risk groups based on five patient-related factors (age, disease stage, serum lactate dehydrogenase [LDH] value, performance status, and the number of sites involved by NHL outside the lymphatic system).[9] However, no such system exists for identifying patients according to different cost profiles incurred, nor has it ever been tested whether the IPI is capable of doing this. This is most probably due to the fact that most cost analyses in NHL have only been based on small series.[10] Therefore, we performed a cost analysis in a group of 374 aggressive NHL patients, examining whether associations between the IPI risk groups with total treatment costs could be identified. In addition, the presence of *B-symptoms* (night sweats, fever, weight loss) at diagnosis was tested as a predictive variable, as we hypothesized that patients with disease-related symptoms might require more supportive care.

In order to facilitate the applicability of our results to other settings, we complied with all methodological requirements enhancing the potential to generalize the results of economic analyses in lymphomas, as reported elsewhere.[10] The most important of these requirements is separate presentation of resource use and unit costs, which enable readers to redo calculations for their own settings.

Patients

This retrospective study was based on data from patients with newly diagnosed aggressive NHL of intermediate or high-grade malignancy according to the Working Formulation, groups D-H[11] (the only histology system that was applied in all study subjects in the years included in this study), Ann-Arbor stage II-IV (disseminated disease),[12] who underwent standard first-line CHOP chemotherapy between 1993 and 2001 (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). In the years covered by this analysis, two randomized controlled trials (RCT) were performed in patients with aggressive NHL. Firstly, the HOVON (Dutch Working Group on Adult Haemato-Oncology) NHL-25 trial compared CHOP with CHOP + prophylactic administration of granulocyte colony-stimulating factor (G-CSF) in patients ≥65 years, in order to investigate whether G-CSF could reduce the severity and duration of leukopenia and infections, problems which often necessitate reduction of the chemotherapy doses.[13] Secondly, patients 15-65 years could be included in the HOVON NHL-26 trial, which compared 8 courses of CHOP to 6 intensified courses of CHOP (14 days cycle interval; higher cyclophosphamide and doxorubicin doses) + G-CSF, under the hypothesis that the exposure of tumor cells to several non-cross-resistant drugs at the maximum tolerated dose, given as early as possible, may circumvent the development of drug resistance.[14] In our analysis, patients from these two RCT were included alongside patients who received CHOP according to standard practice. Two age groups were defined for the analysis, based on the age threshold that the IPI uses: younger patients (<60 years) and elderly patients (>60 years).[9] The aim was to include approximately 200 patients in both groups (number set by practical considerations). Patients were selected from consecutive lists by hematologists from 15 hospitals. Patients with lymphoblastic lymphomas were not included because of a different prognosis. The patients evaluated in this study did not receive rituximab or recombinant human erythropoietin.

Cost analysis

Costs were calculated from the start of first-line treatment until 2 years later. Up to 4 phases per patient were distinguished. All patients underwent first-line treatment (TR1). Unless 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 for 2 years following start of first-line treatment, 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, unless the patient had died during or immediately after treatment. FU2 lasted until the date *2 years after the 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 administered during first-line treatment*. The costs of G-CSF were ignored, given the two RCT in which half of the patients received G-CSF by default. If not mentioned, reported costs relate to total costs excluding G-CSF. For the validity of our calculation, it is important to note that the recommended diagnostic and therapeutic modalities in the protocols of both RCT were the same as those mentioned in the Dutch NHL guidelines.[15] So, except for the costs of G-CSF, no additional costs were expected in the patients treated according to either of these RCT.

The cost analysis was performed from the hospital perspective,[16] and therefore based on all medical resource use generated within the hospital in the 2-year time frame. Data were collected from anony-

mous databases, generated by administrative departments of the participating hospitals. Drug use at home (of medication prescribed by the hematologist) was also included, and estimated from notes in the patients' records. Only NHL-related resource use was recorded; resource use for co-morbidity was not recorded. For the most important items within the resource use, separate unit costs were calculated (Euro, price level 2003) reflecting full hospital costs.[17,18] To determine these unit costs, we applied the micro-costing method.[19] Unit costs, as calculated on the basis of financial data from five of the participating hospitals, were: inpatient hospital day €356 of which 57% for personnel costs (P), 14% for material costs (M), and 29% for overhead costs (O); hematology outpatient visit €68 (P80%, M4%, O16%); other outpatient visit €62 (P80%, M4%, O16%); day care treatment €159 (P44%, M18%, O38%); radiotherapy megavolt session (including preparation costs) €214 (P62%, M15%, O23%); lymph node biopsy under general anesthesia €621 (P46%, M31%, O23%); procedural costs (harvesting, freezing and thawing transplant) of peripheral blood stem cell transplantation (PBSCT) €2495 (P36%, M44%, O20%). For items with low costs or a minor influence, charges were used as approximations, as they were assumed to reflect actual costs appropriately.[17] Costs of medication were based on Dutch wholesale prices.[20] Costs in the second year were discounted at a recommended rate of 4%.[21]

Specific details on the resource use, such as the reasons for hospitalizations, were extracted from the patients' clinical records and daily nursing reports.

Survival analysis

Although the cost analysis was restricted to a 2-year time horizon, for the survival analysis, patients were followed as long as possible. Overall survival time was calculated from start of first-line treatment onwards.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 11.0.1. To determine univariate associations between patients' characteristics and costs, total costs were compared by the non-parametric bootstrap test (1000 replications). This test is recommended for health care economic evaluations, given that cost distributions are almost always skewed and that the bootstrap test is robust with regard to the sample size distribution.[22,23] Univariate and multivariate regression analyses were performed on the natural logarithm of the original costs, 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. Overall survival was estimated by the Kaplan-Meier method.[24]

Patients' characteristics and survival

The characteristics of the 374 patients are shown in Table 1. Overall survival is presented in Figure 1.

Treatment characteristics

Table 2 presents the characteristics of the first-line treatment. Younger patients received an average of 6.82 cycles of CHOP chemotherapy, whereas the elderly patients received an average of 6.22 cycles (p=0.001). The majority of patients received >6 cycles, as recommended. Dose reduction was more frequently applied in elderly patients (34.4% vs. 15.1%, p=0.001).

Table 3 shows the order of phases that patients underwent during the evaluated 2-year time horizon and the number of patients who went through these phases. The lower survival rates of elderly patients, illustrated by Figure 1, explains why the mean follow-up duration mentioned in Table 4 was shorter for elderly patients than for younger patients.

Baseline cost analysis

Table 4 presents resource use and costs of the first-line treatment (TR1) and the consequent follow-up (up to 2 years, undiscounted) according to the intention-to-treat principle, implying that the mean follow-up costs were calculated on the basis of the initial cohorts of 185 younger patients and 189 elderly patients. *Follow-up total* in Table 4 is therefore the sum of *Follow-up 1* (FU1), *Second-line treatment* (TR2), and *Follow-up 2* (FU2).

Table 4 shows that mean costs of TR1 without G-CSF were €10047 (younger patients) vs. €12232 (elderly). The difference was caused by hospitalization costs, as elderly patients were hospitalized more often during TR1. Costs of FU1 were €3523 (younger patients) vs. €4363 (elderly) for average FU1 durations of 363 and 312 days, respectively.

Total 2-year costs (excluding costs of G-CSF administered during TR1) were €24370 (95%CI €21370-€27370) in younger patients and €21234 (95% CI €19057-€23411) in elderly patients. When costs of the second year were discounted, total costs amounted to €24132 (95%CI €21170-€27092), and €21095 (95%CI €18944-€23247), respectively.

When averaged over all patients initially treated, mean costs of second-line treatments were lower in elderly patients (Table 4). This is due to the fact that more younger patients (n=68) than elderly patients (n=48) underwent second-line treatments. Costs of patients who underwent second-line treatments are specified in Table 5 (costs for one elderly patient who underwent high-dose chemotherapy and PBSCT are

Table 1. Patients' 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%)
WF malignancy grade			
D	20 (10.8%)	22 (11.6%)	42 (11.2%)
E	12 (6.5%)	20 (10.6%)	32 (8.6%)
F	7 (3.8%)	21 (11.1%)	28 (7.5%)
G	76 (41.1%)	66 (34.9%)	142 (38.0%)
H	22 (11.9%)	28 (14.8%)	50 (13.4%)
only reported to be 'intermediate grade'	37 (20.0%)	27 (14.3%)	64 (17.1%)
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			
< 1× normal	112 (61.2%)	91(48.4%)	203 (54.7%)
> 1× 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 during the past 6 months. * 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.*

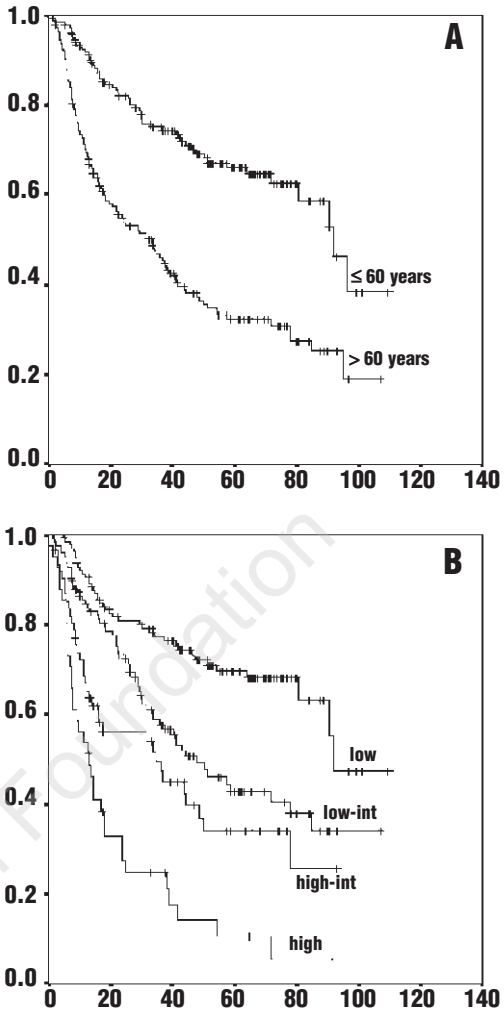

Figure 1. Overall survival from the start of treatment onwards (months), divided by age (A) and IPI risk group (B).

not reported). Costs of chemotherapy as second-line treatment were comparable among younger and elderly patients. Costs of cytostatics were relatively high in elderly patients because of the large proportion of patients receiving expensive regimens. Chemotherapy was followed by radiotherapy in two patients in each group. There was no agreement on second-line chemotherapy: 12 different regimens were applied in younger patients, and 22 different regimens in elderly patients. The most frequently applied regimens were DHAP (cisplatin, cytarabine, dexamethasone) - VIM (etoposide, ifosfamide, methotrexate) - DHAP (25.1%), DHAP only (23.5%), and IMVP (ifosfamide, methotrexate, etoposide) (29.4%) in younger patients. In elderly patients, the most frequently applied regimens were ProMACE-MOPP (prednisone, methotrexate with leucovorin, doxorubicin, cyclophosphamide, etoposide, vincristine, procarbazine, mechlorethamine) (14.6%) and COAP (cyclophosphamide, vincristine, cytosine arabinoside, prednisone) (10.4%).

Mean monthly costs of *regular* follow-up were calculated on the basis of data for patients who spent their entire FU1 in complete remission after first-line chemotherapy, and who reached the scheduled end-

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)
Any hematopoietic growth factor administered*		
In case of trial treatment	51.3%	48.1%
In case of no trial treatment	7.2%	19.2%

**During at least 1 chemotherapy cycle.*

Table 3. Consequence of treatment phases within the 2-year time horizon.

Phase	*Order of phases within the evaluated 2-year time horizon and the number (%) of patients who had these disease courses*							*Total per phase**	
								Younger pts.	*Elder pts.*
First-line treatment	X	X	X	X	X	X	X	185	189
Follow-up 1	X	X	X	X	–	–	–	146	161
Second-line treatment	–	–	X	X	–	X	X	68	48
Follow-up 2	–	X	–	X	–	–	X	46	28
Number (%) of patients									
Younger patients	109 (59%)	2 (1%)	15 (8%)	20 (11%)	6 (3%)	9 (5%)	24 (13%)	185	
Elderly patients	118 (62%)	6 (3%)	19 (10%)	18 (10%)	17 (9%)	7 (4%)	4 (2%)		189

point of the 2-year time frame of this analysis (84 younger patients + 64 elderly). These costs amounted to €191 (median €105, 95%CI €121-€262) in younger patients, and €195 (median €87, 95% CI €115-€274) in elderly patients. The main cost drivers in these amounts were hospital days (younger patients 33%, elderly 44%), radiology diagnostics (younger patients 27%, elderly 14%), hematology outpatient visits (younger patients 13%, elderly 13%), and laboratory diagnostics (younger patients 10%, elderly 8%).

Univariate analysis of cost determinants

Table 6 shows the univariate associations of treatment costs with individual patient-related 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)favorable 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 unfavorable 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, unfavorable performance status and >1 extranodal sites. 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 LDH with 2-year costs.

Since Tables 4 and 5 demonstrated hospitalization costs were the main cost drivers of the total expenditure, we repeated these univariate regression analyses with the total number of hospital days as the dependent variable. The results of these analyses were almost similar to those of the univariate regression analyses shown in Table 6 (data not shown), with the only difference being that the variable *LDH* lost its significance, whereas *performance status* became highly significant, both with regard to first-line hospital days.

Not all variables are predictive for total 2-year costs because more younger than elderly patients underwent second-line treatments and second-line treatment costs varied considerably (Table 5).

The lower part of Table 6 shows the total costs according to IPI risk groups, demonstrating that both the standard IPI and the age-adjusted IPI are able to distinguish different first-line treatment costs according to risk group. This was confirmed by univariate regression analysis on the natural logarithm of the 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 were statistically significant (intercept b=8.828, se=0.061, p=0.000; IPI risk group b=0.147, se=0.041,

Table 4. Mean (median) resource use and costs (Euro) 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)
Hematology 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 in days	146 (158)	152 (149)	363 (489)	312 (294)	37 (0)	39 (0)	62 (0)	15 (0)	462 (559)	366 (471)
Costs										
Hospital days	2559 (0)	4699 (2490)	1262 (0)	2558 (0)	3843 (0)	1240 (0)	465 (0)	484 (0)	5570 (0)	4283 (0)
Hematology outpatient visits	258 (204)	272 (204)	347 (339)	324 (339)	106 (0)	115 (0)	112 (0)	26 (0)	565 (474)	465 (406)
Other outpatient visits	65 (0)	66 (0)	86 (0)	86 (0)	30 (0)	20 (0)	18 (0)	4 (0)	134 (62)	111 (0)
Day care treatments	1060 (1111)	885 (952)	36 (0)	27 (0)	190 (0)	140 (0)	26 (0)	12 (0)	252 (0)	178 (0)
Radiotherapy	625 (0)	539 (0)	35 (0)	65 (0)	50 (0)	115 (0)	56 (0)	15 (0)	141 (0)	195 (0)
Pathology diagnostics	115 (0)	105 (0)	130 (0)	75 (0)	103 (0)	47 (0)	15 (0)	11 (0)	247 (0)	134 (0)
Laboratory diagnostics	422 (263)	471 (417)	280 (182)	244 (168)	283 (0)	108 (0)	56 (0)	39 (0)	619 (375)	391 (254)
Microbiology diagnostics	72 (0)	78 (0)	43 (0)	30 (0)	258 (0)	22 (0)	12 (0)	11 (0)	313 (0)	64 (0)
Radiology diagnostics	820 (693)	904 (863)	817 (635)	446 (144)	372 (0)	141 (0)	159 (0)	67 (0)	1347 (154)	654 (376)
Nuclear diagnostics	194 (0)	195 (0)	130 (0)	41 (0)	913 (0)	119 (0)	31 (0)	3 (0)	1075 (0)	163 (0)
Other diagnostics	69 (0)	88 (0)	69 (0)	97 (0)	264 (0)	44 (0)	8 (0)	10 (0)	341 (0)	151 (0)
Blood components	328 (0)	402 (0)	131 (0)	78 (0)	0 (0)	92 (0)	159 (0)	39 (0)	290 (0)	209 (0)
PBSCT	0 (0)	0 (0)	0 (0)	0 (0)	391 (0)	13 (0)	0 (0)	0 (0)	391 (0)	13 (0)
Cytostatics	3005 (3205)	2516 (2584)	0 (0)	0 (0)	1593 (0)	1331 (0)	0 (0)	0 (0)	1593 (0)	1331 (0)
G-CSF	1652 (0)	2264 (0)	0 (0)	0 (0)	379 (0)	98 (0)	0 (0)	0 (0)	379 (0)	100 (0)
Antibiotics	271 (0)	476 (8)	39 (0)	111 (0)	275 (0)	104 (0)	96 (0)	26 (0)	410 (0)	240 (0)
Other drugs	183 (4)	534 (189)	120 (0)	181 (0)	139 (0)	145 (0)	114 (0)	20 (0)	372 (7)	346 (15)
Total costs										
Excluding G-CSF	10047 (7454)	12232 (10175)	3523 (1735)	4363 (1360)	8810 (0)	3796 (0)	1327 (0)	768 (0)	13660 (4434)	8927 (3408)
95% CI	9016-11132	11150-13451	2472-4575	3137-5588	6566-11055	2560-5032	718-1934	235-1302	11235-16562	7036-10630
Including G-CSF	11726 (8873)	14564 (12669)	3523 (1735)	4363 (1360)	9190 (0)	3895 (0)	1327 (0)	768 (0)	14039 (4434)	9026 (3408)
95% CI	10515-12938	13228-15901	2472-4575	3137-5588	6875-11505	2618-5172	718-1934	235-1302	11562-17028	7111-10755

**Complications could be related to NHL or to chemotherapy; †Sum of 'Follow-up 1', 'Second-line treatment', and 'Follow-up 2'; PBSCT: peripheral blood stem cell transplantation; G-CSF: granulocyte colony-stimulating factor.*

p=0.000). Table 6 presents 2-year costs according to IPI risk group. Univariate regression analyses showed that the predictive value of the IPI standard score with regard to 2-year costs is dramatically lower (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 were less obvious than those for first-line treatment. Again, this is due to differences in numbers and types of second-line treatments applied. The positive linear relationship between IPI risk group and total costs is primarily caused by a larger number of days of hospital care required in the unfavorable risk groups. Whereas the relative contributions of all other cost items remained

Table 5. Mean (median) resource use and costs (Euro) of second-line treatments, according to per-protocol principle.

	Younger patients		*Elderly patients*	
	Chemotherapy (n=39)	*High-dose chemotherapy + PBSCT (n=29)*	*Chemotherapy (n=42)*	*Radiotherapy (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)
Hematology 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	6990 (6402)	15119 (13516)	5191 (2490)	3273 (0)
Hematology outpatient visits	252 (135)	339 (339)	494 (339)	189 (204)
Other outpatient visits	62 (0)	108 (62)	85 (0)	37 (0)
Day care treatments	549 (159)	471 (159)	627 (318)	0 (0)
Radiotherapy	191 (0)	66 (0)	76 (0)	3718 (4274)
Pathology diagnostics	267 (85)	294 (170)	181 (101)	276 (271)
Laboratory diagnostics	700 (600)	861 (635)	433 (341)	235 (182)
Microbiology diagnostics	426 (91)	1073 (815)	101 (0)	6 (0)
Radiology diagnostics	862 (751)	1217 (1022)	583 (319)	426 (399)
Nuclear diagnostics	1750 (238)	3471 (1268)	530 (0)	36 (0)
Other diagnostics	493 (0)	1021 (770)	197 (22)	17 (0)
Blood components	0 (0)	0 (0)	400 (0)	84 (0)
PBSCT	0 (0)	2495 (0)	0 (0)	0 (0)
Cytostatics	3775 (3004)	5081 (4609)	5879 (2967)	0 (0)
G-CSF	652 (0)	1545 (1248)	445 (0)	0 (0)
Antibiotics	424 (92)	1188 (334)	468 (3)	22 (0)
Other drugs	225 (153)	584 (522)	610 (233)	357 (0)
Total costs				
Excluding G-CSF	16968 (13688)	33387 (27073)	15855 (13347)	8676 (6228)
95% CI	13225-20709	26271-40502	12222-19487	2578-14774
Including G-CSF	17619 (13877)	34932 (29238)	16300 (13456)	8676 (6228)
95% CI	13762-21476	27885-41978	12515-20085	2578-14774

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

constant or even decreased, the relative contribution of hospitalization costs to the first-line treatment costs according to standard IPI (Table 6) rose from 22% (low risk), 34% (low-intermediate), 38% (high-intermediate), to 45% (high risk). For first-line treatment costs according to age-adjusted IPI, these percentages were 22%, 30%, 38%, and 47%, respectively.

Multivariate analysis of cost determinants

Table 7 shows the results of the ordinary least squares regression analysis on the natural logarithm of the total costs. When combined in one model, three out of five IPI variables remained significant predictors of total costs (age, LDH, and extranodal sites). When the variable *B-symptoms* was added (not shown), this

Table 6. Mean costs (Euro, 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	10420	9555-11404		20120	18329-22098	
present	12608	11280-13996		26916	23348-30598	
difference	2188†	569-3955	0.002	6797†	2809-10941	0.000
IPI Age						
<60 years	10059	9024-11138		23823	21189-26798	
>60 years	12268	11136-13437		21114	19003-23336	
difference	2209†	540-3866	0.006	-2709	-6341-860	0.469
IPI Ann Arbor stage						
II	9718	8732-10856		19236	16603-22149	
III/IV	11782	10906-12693		23868	21724-26152	
difference	2065†	692-3438	0.032	4632†	1080-8281	0.018
IPI Serum LDH						
< 1x normal	10517	9480-11611		22287	19736-24960	
> 1x normal	11980	10912-13169		22690	20295-25286	
difference	1462‡	-143-2972	0.012	403	-3149-3933	0.444
IPI Performance status						
ambulatory	10835	10049-11682		21971	20074-23854	
not ambulatory	14149	11469-17305		27362	22778-32470	
difference	3314†	561-6507	0.055	5391†	312-10688	0.025
IPI Number of extranodal sites						
< 1 site	10476	9675-11293		21611	19674-23594	
> 1 site	13832	11873-15915		26082	21933-30197	
difference	3357†	1162-5389	0.002	4472‡	-50-8884	0.022
IPI Standard score*						
low (0-1)	9366	8328-10440		21398	18605-24698	
low-intermediate (2)	11251	10055-12633		23305	20241-26398	
high-intermediate (3)	12604	10417-14747		22250	18329-26630	
high (4-5)	15253	12918-17810	nc	24694	20269-29779	nc
IPI Age adjusted score*						
low (0)	9556	8135-11172		17375	14345-20930	
low-intermediate (1)	10443	9347-11592		22948	20148-25758	
high-intermediate (2)	12555	11178-14084		24356	21353-27773	
high (3)	15221	11406-19185	nc	24396	18619-30543	nc

*G-CSF: granulocyte colony-stimulating factor; CI: confidence interval; IPI: International Prognostic Index for aggressive NHL; LDH: lactate dehydrogenase, nc: not calculated. †Significant difference according to bootstrap test. ‡Very close to significant difference according to bootstrap test. * 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.*

became the most significant predictor, whereas the variable *LDH* lost its significance. Again, 2-year costs turned out to be less predictable, as performance status was the only significant variable in this multivariate model (Table 7). When the variable *B-symptoms* was added (*not shown*), this was the only significant variable. When applying a multivariate model instead of 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 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).

Discussion

We performed a descriptive cost analysis in aggressive NHL on costs of first-line treatment and 2 years of follow-up, including second-line treatments. We tested whether the IPI variables (age, disease stage, serum LDH value, performance status, number of sites involved by NHL outside the lymphatic system) and

Table 7. Ordinary least squares regression analysis of the logarithm of the total costs (excluding G-CSF).

Independent variables	Dependent variables: log (first-line treatment costs) b (se)	p value	log(total 2-year costs) 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 (favorable) and 1 (unfavorable). G-CSF: granulocyte colony-stimulating factor.

the presence of B-symptoms (night sweats, fever, and/or weight loss) could be used to identify groups of patients with favorable or unfavorable cost profiles. Univariate analyses showed all 5 IPI variables and B-symptoms to be predictive of first-line treatment costs. With regard to 2-year costs, univariate associations were shown with all variables, except for LDH and age. This is due to the variety in number and types of second-line therapies administered in younger and elderly patients, which causes 2-year costs to vary much more than first-line treatment costs. No uniformity in second-line treatments was observed. The risk groups of the IPI (standard index and age-adjusted index) resulting from the 5 individual variables were strongly 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 2-year costs, but the standard IPI was not, for 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 first-line treatment and 2-year costs. In the multivariate analysis, this was the most significant variable, and it was included in all models resulting from step-down regression analysis.

As compared to the IPI risk factors, B-symptoms might seem a relatively *soft* variable and one might therefore wonder whether the reliability of this variable and the reliability of the IPI risk factors are similar. We believe that they are in our analysis, because the data were drawn from specialized hematology centers in which the hematologists know the rules regarding B-symptoms and record this information correctly in the patients' clinical records. It could therefore be determined from the clinical records whether a patient had experienced at least one of the three symptoms required for a positive *B-symptoms score* (night sweats, fever of >38.3 °C, unexplained weight loss of >10% of the original body weight during the past 6 months).

We assume that we have studied a representative sample of patients with aggressive NHL, because the survival of our group (Figure 1B) compares well with the survival of the 2031 patients on which the IPI was based.[9] Approximately 50% of our group of patients underwent first-line treatment according to a clinical trial protocol, but we do not believe that this is a limitation, since both trials compared standard CHOP to a CHOP-variant: vs. G-CSF in elderly patients (HOVON NHL-25 trial), and vs. intensified CHOP+G-CSF (HOVON NHL-26 trial) in younger patients. In the NHL-25 trial, no survival differences were shown and, more importantly for our analysis, the number of severe infections and the duration of hospital stay were equal in the two arms.[13] It was, therefore, recommended that standard prophylactic G-CSF is not applied, although many clinicians routinely do prescribe growth factors despite the lack of evidence in the literature supporting this practice.[25] In the cost analysis performed alongside that trial, the only cost difference between the arms involved the costs of the G-CSF itself.[26] This supports the validity of our results that are based on both trial and non-trial patients. The final analysis of the NHL-26 trial has not been performed yet, so no definite conclusions about the validity of this sample can be drawn. However, in a German trial also comparing CHOP to intensified CHOP+G-CSF, the side-effect profiles were quite similar between the treatment arms.[27] Most importantly, however, the percentages of side effects in these younger patients were, in any case, very low supporting the assumption that costs in these patients will also be comparable between the two arms. We excluded the costs of G-CSF administered during first-line treatment from our calculation of total costs, because in the two clinical trials half of the patients received G-CSF by default, and therefore these costs would have been misleading. When G-CSF prophylaxis is used, approximately €1100 per chemotherapy cycle must be added to the costs. According to a recent review,[10] there is only one earlier publication available on the description of first-line treatment costs of aggressive NHL with which our results can be compared. That study[28] was, however, based on much smaller groups of patients and it had another central question. It concluded that the costs of NHL patients treated in clinical trials (which were the same trials considered in that earlier study) were in the same range as the costs of NHL patients treated according to standard local practice.

Second-line treatment costs in NHL will always be less predictable than first-line treatment costs, unless

one type of second-line chemotherapy is, in the future, demonstrated to be superior over all others. For example, regional preferences on the type of second-line chemotherapy still exist in the Netherlands. Indeed, in the recent Dutch national guidelines on NHL, no specific second-line chemotherapy regimen is recommended (if the patient is not eligible for stem cell transplantation), precisely because no regimen has been proven to be superior to others.[15] One might, therefore, wonder why we present cost data based on a variety of second-line treatments. The reason is that such information is needed for cost-effectiveness evaluations but so far, except for stem cell transplantation, there is hardly any cost information available on second-line NHL treatments.[10] An example that underlines this need is the recent analysis of Kuruvilla in which CHOP + rituximab (R-CHOP) was concluded to be economically attractive, mainly by reducing the need for second-line therapy.[29] Although it was not the primary aim of our analysis, our data also enabled us to analyze mean costs according to the variable *death within the 2-year time frame*. This revealed that, both in younger and elderly patients, total 2-year costs were significantly higher when the patient died within the 2-year time frame of the analysis (€37094 vs. €21468, and €25449 vs. €17905, respectively), due to the higher percentages of patients who underwent second-line therapy among those who died within this time frame than among those who survived this interval: 84% vs. 27% in younger patients, and 35% vs. 17% in elderly patients. This underlines the conclusion reached by Kuruvilla and colleagues, based on their modeling study: although new treatments (e.g. R-CHOP) might be more expensive at first sight, they can be economically attractive in the end, if they can lead to higher survival rates and higher response rates (and consequently to lower rates of second-line therapies). It is important to determine whether our results can be generalized to other settings, since the analysis was based on Dutch unit costs. Many cost analyses in NHL have not presented their results in such a way that they can be used in other settings,[10] particularly because of the failure to provide sufficient detail concerning the resource use and the applied unit costs. When applying models to particular settings, it might be necessary to make new calculations based on local unit costs or resource use numbers. Since we have published our results in order for others to use them (for example in economic modeling studies, like the study by Groot and colleagues,[30] we have provided resource use (Tables 4 and 5) and unit costs in detail and for different phases. Estimates are significantly facilitated by the availability of this kind of information. Furthermore, it is important to note that the general findings of our study are very probably applicable to many countries, irrespective of absolute cost levels, because in all countries, items of unit costs of resource use actually only express the relative weight of one resource use item over another. Although the absolute prices might be different, a day of hospital care will always be much more expensive than a CT-scan, which in turn will be much more expensive than a serum hemoglobin assay. It is therefore highly plausible that in a comparable analysis in another country, the prognostic significance of the IPI factors for the total costs would also have been established, a possibility favored by the fact that CHOP treatment is a standardized treatment worldwide.

Finally, given recent developments the validity of our results should be discussed. After 30 years of CHOP dominating the field of first-line treatment for aggressive NHL, R-CHOP is now considered to be the new standard treatment regimen.[31] In a recent cost-effectiveness study, the only difference in first-line treatment costs between the CHOP and R-CHOP regimens was the cost of rituximab itself.[30] The addition of rituximab to CHOP did not influence any of the other cost categories. The costs of managing side effects in the first-line treatment also remained stable, implying that our results are valid for the future. Groot and colleagues found that the cost of the rituximab addition was approximately €15500 (similar amounts were determined in an Italian study).[32] Rituximab is, therefore, a cost determinant on its own within the R-CHOP scheme, as compared with the CHOP costs of €10000-€12000 that we calculated. As a result, adding the rituximab costs would only blur relative differences between the costs of the several prognostic groups that we calculated. We therefore recommend applying the formulas we have presented and simply adding the costs of rituximab (approximately €2100 per cycle) to these formulas, particularly because the costs of rituximab itself are relatively stable and do not vary greatly between patients. The costs of rituximab actually only depend on the number of chemotherapy cycles, which should be 6 to 8 in any patient, irrespective of IPI risk group. In conclusion, we show that the 5 IPI variables, the two IPI risk group variables, and the presence or absence of B-symptoms can be used to distinguish groups of patients with aggressive NHL according to cost profiles. In addition to its traditional use of estimating chance of survival, the IPI can therefore be used to identify subgroups of patients in whom new treatment modalities may result in the largest cost-effectiveness increases. The detailed information presented in this paper can serve as a basis for comparisons, in order to determine whether new pharmaceuticals are cost-effective. This is particularly of value for economic modeling studies that are usually based on so-called *Markov models*, the results of which are highly dependent on reliable input values. For examples in which data like ours were used in such studies, readers are referred to the recent analyses by Groot,[30] Berto[32] and Kuruvilla.[29]

Because of the cost impact of rituximab and other expensive treatment modalities coming onto the scene (e.g. radiolabeled monoclonal antibodies), we expect more of such analyses to appear in the near future. Not only the costs we reported, but also our distribution of patient characteristics and the mean duration of treatment phases can be used in such analyses, as they were drawn from a population-based sample. We found that the higher costs in patients with unfavorable characteristics were particularly caused by the days of hospitalization care required, which was confirmed by additional regression analyses. New pharmaceuticals for aggressive NHL, which are successful in reducing complications and NHL-related hospitalisations, increasing survival rates, and decreasing the need for second-line treatment may, therefore, improve cost-effectiveness.

MvA managed the data collection process, performed the analyses and wrote the manuscript and is therefore the first author. PS and LV, as hematologists, had major roles in the design of the study and interpretation of the data, were the principal investigators of the clinical studies of the patient whose data were included in this analysis, and approved publication of the manuscript. PS is the second author, because of the overall clinical supervision of this project. CU is the leader of the health economics program in the context of which this study was performed, and is therefore the last author, who also approved publication of this manuscript.

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