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Economic evaluation of prophylactic granulocyte colony-stimulating factor during chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma

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A B S T R A C T

Background and Objectives. Treatment with CHOP chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma (NHL) is less effective and accompanied by more adverse effects than in younger patients. The prophylactic use of granulocyte colony-stimulating factor (G-CSF) might improve the results, but increases the costs of treatment. We analyzed the costs of therapy and follow-up of patients with NHL treated with CHOP with or without G-CSF prophylaxis.

Design and Methods. Four hundred and eleven patients were randomized for treatment with CHOP or CHOP+G-CSF. A detailed study of treatment costs from randomization until 3 years of follow-up or death was performed in a subset of 100 out of 389 eligible patients. Because costs during follow-up were independent of the use of G-CSF during treatment, costs of follow-up and second-line treatment were calculated irrespective of the treatment arm.

Results. Total hospital costs for first-line treatment were €12178 [95% CI €10297 – €14059] for CHOP alone and €18356 [95% CI €15807 – €20906] for CHOP + G-CSF. Costs during follow-up showed a wide difference (range €74 – €53925) depending on disease status and choice of treatment in the case of relapse or progression.

Interpretation and Conclusions. The clinical study showed no difference between the treatment arms in response, overall survival or event-free survival, while the costs were significantly higher in the G-CSF arm. We conclude that the addition of prophylactic G-CSF to CHOP chemotherapy is not cost-effective in these patients.

Key words: non-Hodgkin's lymphoma, costs, CHOP, G-CSF, granulocyte colony stimulating factor.

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Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignancy in adults. Its incidence shows a steady increase of 4% per year, both in the USA and Europe.[1,2] The incidence increases with age. Standard first-line therapy for aggressive (diffuse large B-cell, peripheral T-cell lymphoma), disseminated NHL has been CHOP chemotherapy ever since the mid-1970s.[3-5] However, for a long time, this regimen has been considered too toxic for elderly patients.[6,7] Therefore, several chemotherapy regimens were developed to reduce toxicity, but none of these turned out to be as effective as CHOP.[8-12] Presently 50% of elderly patients will obtain a complete remission, although only half of them will be cured.[10-13] Higher age has shown to be a negative prognostic factor for both complete remission and survival.[14] One possible reason for the poor outcome is that elderly patients tolerate combination chemotherapy less well than younger patients do. Elderly patients more often develop leukopenia and as a result infectious complications. Leukopenia often results in postponement of chemotherapy courses and/or dose reduction. This leads to a lower relative dose intensity, which might negatively affect cure rates.[15]

Hematopoietic growth factors, such as recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) and recombinant human granulocyte colony-stimulating factor (rhG-CSF) shorten the duration of neutropenia.[13,16-18] Thus, they have the potential to reduce costs for antibiotics and hospitalization. Furthermore, the cost of prophylactic G-CSF use may be justified if it is compensated for by objective clinical benefits or by a subjectively perceived improvement of the quali-

ty of life. The high incidence of neutropenia and its consequences (infections) are more evident in elderly patients, so these patients might particularly benefit from prophylaxis with growth factors. On the other hand, as the incidence of NHL rises by 4% per year, routine G-CSF use in these patients might result in substantial increases in health care expenses.

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

Design and Methods

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

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

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

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

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

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

Table 1. Main outcomes of the clinical study.

	CHOP n = 192	*CHOP + G-CSF n = 197*	*P value*
Complete response rate	55%	52%	0.63
Overall response rate	83%	85%	0.70
Overall survival at 5 years	22%	24%	0.76
Event-free survival at 5 years	18%	17%	0.52
Progression-free survival at 5 years	24%	25%	0.65
Disease-free survival at 5 years	43%	40%	0.31
Infection WHO grade 3-4*	3%	3%	0.82
Infection WHO grade 2-4*	15%	11%	0.007
Patients experiencing fever	45%	37%	
Median duration of fever in patients with fever, in days (mean)	3 (4.7)	2 (3.0)	
Median days with fever, all patients (mean)	0 (2.1)	0 (1.1)	0.056
Median days on antibiotics (mean)	6 (16)	0 (8)	0.006

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

cedures were multiplied by Dutch charges, as these are proper approximations of the actual unit costs.[24] Costs of medication were based on Dutch wholesale prices.[25] The original base year was 1997 and costs were indexed to 2002 prices using price indices as provided by Statistics Netherlands (*www.cbs.nl*). Total costs were divided into costs of first-line treatment and costs of follow-up. In economics it is assumed that individuals prefer good outcomes to occur sooner rather than later. Thus, to correct for the passage of time, outcomes are discounted, generally at a constant rate. For costs in the 2nd and 3rd year a recommended discount rate of 4% was applied.[23] Because no relation was assumed between the use of G-CSF during first-line treatment and cost during follow-up, this was calculated irrespective of treatment arm and attributed to the treatment outcome.

Statistics

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

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

Results

Main results of the clinical trial

From August 1994 until September 2000, 411 patients were enrolled in the clinical study and 389 of them were eligible for evaluation: 192 patients were randomized to CHOP and 197 patients to CHOP + G-CSF. The relative dose intensity of cyclophosphamide (median 93.9% vs 96.3%, $p = 0.01$) and doxorubicin (median 93.3% vs 95.4%, $p = 0.04$) was significantly higher in the CHOP + G-CSF group and the median duration of antibiotic use was 0 as compared to 6 days in the CHOP group. However, no differences were observed between the treatment groups with respect to overall response or survival. Also, no differences in quality of life could be demonstrated. The patients' characteristics and main outcomes are presented in Table 1. The clinical results have been reported in detail elsewhere.[19]

Representativeness of patients in the cost analysis

One hundred patients were selected for the cost analysis study regardless of and without information

Table 2. Patients' characteristics in the entire clinical study and cost study.

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

**: p = 0.19; °: p = 0.25; #:p = 0.51.*

on their disease status or treatment outcome. Apart from the costs of first-line treatment, the total costs of the three-year study period were expected to be mainly determined by toxicity, disease progression or relapse. The characteristics and the clinical outcome of the 100 patients in the cost analysis were compared with those of the whole clinical study population. No significant differences were observed for any patient characteristic (Table 2). With respect to the clinical outcome, no significant differences were found: 57% of the patients selected for the cost analysis reached a CR. Their overall survival at 1, 2 and 3 years from randomization was 64%, 47% and 39%, respectively. The median survival was 22 months. The event-free survival at 3 years from randomization was 23%. For all 389 patients in the clinical study, the CR rate was 53%, while the overall survival at 1, 2 and 3 years from randomization was 64%, 46% and 37%, respectively. The median survival was 21 months and the event-free survival at 3 years from randomization was 26%. In the total study population 30% of the patients were treated in a university hospital, as compared to 44% in the cost study. As mentioned in the *Methods* section, a correction for this difference was made in the cost calculation weighting the unit costs for their origin. The results presented below only relate to the 100 patients selected for the cost analysis.

Costs of first-line treatment

The mean duration of treatment was 163.1 days (CHOP, range 44-365) versus 152.5 days (CHOP + G-CSF, range 3-287, $p = 0.42$). The mean number of CHOP cycles was 6.2 in the CHOP arm (range 2–8) and 5.9 in the CHOP + G-CSF arm (range 1–8) The median number of CHOP cycles was 6 in both treatment groups. Three out of 50 patients randomized to CHOP alone received G-CSF for an average of 8.3 days (range 1-23). One out of 50 patients randomized to CHOP + G-CSF never received G-CSF. This patient died on day 2 after randomization. The mean number of days with G-CSF in the remaining 49 patients in the CHOP + G-CSF group was 57.3 (range 10-88). The total number of hospital days was 15.0 (CHOP, range 0-94) versus 17.2 (CHOP + G-CSF, range 0-73, $p = 0.56$). Reasons for hospitalization were all related to NHL and/or CHOP treatment. In both treatment groups, 30 out of 50 patients (60%) were hospitalized during their first cycle of CHOP. Inpatient treatment for the first CHOP cycle occurred more commonly in community hospitals (77%) than in university hospitals (39%). Because the patients in both treatment arms were equally divided over the community and university hospitals, this did not influence the cost comparisons. Fourteen patients (6 CHOP vs. 8 CHOP + G-CSF) received radiotherapy during or after completion of chemotherapy. During treatment, 29 patients treated with CHOP received red blood cell transfusions, (mean 5.0 units, median 4) compared to 18 patients treated with CHOP + G-CSF (mean 5.8, median 4). Platelet transfusions were required in 3 patients in the CHOP arm (mean 3.3 units) and in 2 patients in the CHOP + G-CSF arm (mean 6.0 units).

Total average hospital costs (in- and outpatient, including medication used at home) for first-line treatment amounted to €12178 [95% CI €10,297-€14059] for patients treated with CHOP and €18,356 [95% CI €15,807–€20,906] for patients treated with CHOP + G-CSF.

Data on costs outside the hospital were collected through questionnaires completed by patients who participated in the quality of life study. Response rates to questionnaires during first-line therapy were high: 90% of pre-treatment questionnaires were returned, 98% after the 2nd course, 97% after the 4th course and 96%

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

	Resource use		*Costs in Euro*		
	CHOP N = 50	*CHOP+G-CSF N = 50*	*CHOP*	*CHOP + G-CSF*	*P value*
Hospital days	15.2 (10)	17.3 (8)	4,998 (3,606)	5,670 (2623)	0.73
Day care treatments; chemotherapy	5.2 (6)	4.4 (6)	666 (768)	562 (768)	0.14
Day care treatments; transfusion	0.6 (0)	0.4 (0)	83 (0)	47 (0)	0.07
Outpatient visits; hematologist	10.44 (10)	9.00 (10)	603 (578)	520 (578)	0.25
Outpatient visits; other	1.22 (0)	1.08 (0)	71 (0)	63 (0)	0.42
Units of red blood cells	2.9 (2)	2.1 (0)	553 (381)	398 (0)	0.04
Units of platelets	0.20 (0)	0.24 (0)	46 (0)	55 (0)	0.66
Radiotherapy	6 patients	8 patients	296 (0)	395 (0)	0.57
Laboratory tests			841 (741)	768 (606)	0.45
Other diagnostic procedures			1,351 (1,175)	1,260 (1,213)	0.67
Chemotherapy			1,846 (1,830)	1,755 (1,831)	0.54
Antibiotics			420 (161)	197 (10)	< 0.01
Other medication			292 (279)	322 (279)	0.88
Total hospital costs, excl. G-CSF			12,122	12,052	0.49
G-CSF	0.5 (0)	57 (60)	56 (0)	6,304 (6,741)	< 0.001
Total hospital costs, incl. G-CSF			12,178	18,356	< 0.001
General practitioner, incl. traveling costs	3.9 (2)	4.1 (2)	73 (37)	77 (37)	0.89
Community nurse (hours)	2.5 (0)	7.2 (0)	90 (0)	253 (0)	< 0.001
Home help (hours)	10.5 (0)	14.8 (0)	207 (0)	290 (0)	0.27
Total treatment costs			12,548 (11,726)	18,976 (17,788)	< 0.001

after the 6th course. Prior to treatment no differences in resource use were present between the two study arms. During treatment, the number of visits to the general practitioner and the use of assistance with housekeeping were comparable in both groups. Patients in the CHOP + G-CSF arm had significantly more support from a community nurse: 7.2 hours versus 2.5 hours in the CHOP arm ($p < 0.01$). Before starting treatment, 97% of patients did not use support from a community nurse. During treatment, 89% of patients in the CHOP arm and 55% of patients in the CHOP + G-CSF arm did not get home nursing assistance (p=0.0001). One third of patients in the CHOP + G-CSF group needed assistance from a community nurse for the G-CSF injections. Although the amount of informal care was asked about in the questionnaires, it was not possible to translate the obtained information into costs. The patients were not able to estimate the number of hours of informal care exactly. Common answers were: *if needed*, *much*, *sometimes* and *always*. Therefore, informal care is only described without valuing it. Before the start of treatment, 59% of patients received informal care. This percentage remained stable during CHOP courses (64% after 2nd course, 60% after 4th course and 61% after 6th course) and there were no differences between the two treatment arms. All resource uses and costs during first-line treatment are shown in Table 3.

Costs of follow-up

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

developed a relapse after CR (n = 18), patients who disease progressed after PR (n = 13) and one patient who experienced a relapse during treatment.

The average costs for patients without relapse/progression were €5832 (median €1516; range €74–€50690). The mean discounted costs were €5686. The main cost drivers were hospitalization (62%), outpatient visits (11%) and diagnostic procedures (9%). Reasons for hospitalization for these patients in disease remission were: cardiac failure after CHOP (n = 4), sepsis/fever immediately after CHOP (n = 2), suspected relapse (n = 1), paralytic ileus after CHOP (n = 1), acute secondary leukemia (n = 1) and waiting for a place in a nursing home (n = 1).

The 48 patients in the relapse/progression group together had 52 cases of disease recurrence or progression. Eight patients did not receive any second-line treatment and the other 44 episodes were treated by 26 different treatment options, varying from radiotherapy, chlorambucil, CHOP-like regimens, ifosfamide-based regimens and various other chemotherapy regimes. None of these elderly patients received high-dose chemotherapy followed by stem cell transplant. As a result of the divergent treatments, the costs showed wide variations. The mean follow-up costs for these patients were €15224 (median €14281; range €1115 – €53925). The mean discounted costs were €14811. The main cost drivers were days of hospitalization (46%), medication (18%) and diagnostic procedures (9%). The most common reasons for hospitalization were administration of second-line chemotherapy and general illness.

Costs outside the hospital were collected until the 18 month of follow-up. For patients in remission, the average costs per month were €58: €12 for visits to the general practitioner, €6 for the community nurse and €40 for home assistance. For patients in progression or relapse, the average costs per month were €67: €28 for visits to the general practitioner, €30 for community nursing and €9 for home help. Assuming that the average monthly resource use during this period is also valid for the period in which no data were collected, the average costs were €1384 (discounted €1330) for patients who remained in remission and €883 (discounted €849) for patients who experienced relapse or progression (patients with progression or relapse on average died earlier, so the total costs were lower).

Cost-effectiveness

A cost-effectiveness ratio was not calculated. The clinical trial showed no benefits in major outcome measures for either of the treatment options. Since the addition of G-CSF to CHOP induced extra costs of €6178 (costs in hospital + medication, 95% CI of the difference = + €3050/+ €9307)* at no extra benefit, the conclusion that this treatment is not cost-effective compared to standard CHOP seems justified.

Discussion

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

The results of first-line treatment in both arms were identical with respect to CR rate and event-free, disease-free and overall survival. Therefore, a difference in costs during follow-up seems unlikely. We decided not to distinguish follow-up costs according to initial trial arm, but to separate the costs of follow-up in two groups on the basis of response: patients who did not show any relapse or progression and patients who had recurrent or progressive disease. With respect to second-line treatment at the time of disease progression or relapse, a large variation in treatments in these elderly patients was observed. The differences of preferences for second-line treatment among the participating hospitals were reflected in a wide variation of costs during follow-up. From an economic point of view the choice of treatment for elderly relapsing patients might therefore be a very interesting topic for future research. In this study G-CSF had no important clinical benefits in terms of CR rate

**When costs outside the hospital are also considered, the total cost difference is 6428. A 95% CI cannot be calculated for this total difference because the costs outside the hospital were collected from another sample of patients.*

and survival, as has also been reported previously.[16,19,31] The prophylactic use of G-CSF was beneficial in reducing the infection rate, although no reduction in more severe infections (WHO grade III and IV) was observed. G-CSF prophylaxis resulted in fewer antibiotic prescriptions, but no decrease in hospital admissions. The additional costs of G-CSF were only in part counterbalanced by the fewer antibiotic prescriptions, and the overall costs of CHOP + G-CSF were significantly higher than those of CHOP alone. The American Society of Clinical Oncology (ASCO) guidelines on the use of hematopoietic colony-stimulating factors (CSF) do not recommend primary prophylactic CSF. In special circumstances, such as treatment of elderly patients, CSF might be considered, although its benefits have not been determined.[32] The National Comprehensive Cancer Network (NCCN, USA) recommended the prophylactic use of hematopoietic growth factors for patients aged 70 and older.[33] The European Organization for Research and Treatment of Cancer (EORTC) guidelines for the use of CSF in elderly patients with cancer recommend prophylactic G-CSF for all elderly patients receiving curative therapy.[34] These recommendations were largely based on the major reduction in neutropenia observed with G-CSF administration, and the reduced number of neutropenic infections. No randomized study has shown any benefit in survival, or a reduction in toxic deaths. With an expanding older population, and an increasing incidence of NHL, the standard use of prophylactic G-CSF could have major consequences for the health care budget.

The majority of economic studies on the use of prophylactic G-CSF have been performed in the treatment of small cell lung cancer (SCLC). The first clinical placebo-controlled, randomized trial with primary G-CSF prophylaxis showed an impressive reduction in rates of febrile neutropenia (FN), from 77% to 40%. The incidence of hospitalization was reduced by 50%.[35] A cost analysis was performed in a subgroup of patients. Three health care models were used, resulting in different FN risk thresholds for the costs of G-CSF being less than the costs of FN hospitalization: 35% (charge model), 60% (cost model) and 70% (Medicare model).[36] A cost minimization study concluded that with a risk of FN of > 40% the use of G-CSF was cost-effective.[37] Also taking into account indirect costs during FN, a 20-25% risk of FN has been estimated as a threshold in economic models.[38,39] In another clinical study comparing G-CSF prophylaxis with placebo in patients with SCLC the incidence of FN was slightly lower.[40] However, the incidence of FN in the placebo-treated patients in these two studies was considerably higher than in standard clinical practice, in which an incidence of FN of 18-19% is reported.[41,42] Several reviews on the economic impact of prophylactic G-CSF in the treatment of SCLC have been published.[43,44] It is clear that the cost-effectiveness of primary G-CSF prophylaxis depends on several factors. It is suggested that elderly patients in particular may benefit from the primary G-CSF prophylaxis.[45] In a survey on the use of prophylactic G-CSF in the USA it was reported that the ASCO guidelines on this topic are supported by > 90% of respondents.[46] In practice, the use of colony-stimulating factors was found to deviate from the ASCO guidelines, with wide variation between different oncology practices and even at the level of individual oncologists within a practice.[47] A retrospective study on the treatment of aggressive NHL in a large group of patients reported that 17% of all patients experienced FN, 21% of patients aged > 65 years did so. Only 8% received early G-CSF (started at cycle 1 or 2).[48] Three small studies suggested that adding prophylactic G-CSF to standard chemotherapy would lead to a more cost-effective treatment as compared to standard chemotherapy without G-CSF, particularly in elderly patients.[18,49,50] A larger French study that randomized younger patients undergoing 4 cycles of ACVBP or NCVBP chemotherapy (doxorubicin or mitoxantrone, cyclophosphamide, vindesine, bleomycin, methylprednisone) to lenograstim or placebo concluded that adding G-CSF resulted in lower costs, given a lower number of infections and few days spent in hospital.[51] However, the costs of lenograstim itself were left out of consideration. The cost benefit is no longer present if G-CSF costs are added.

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

JKD: as clinician involved in the conception and design of the study, wrote the article and approved the publication; IB: researcher of the Institute of Medical Technology Assessment; (iMTA): partner in the concept of the study, analyzed and interpreted the data, revised the article and approved the publication; BvdH: statistician, involved in design of the study and interpretation of data, revised the article and approved its publication; MvA: researcher of iMTA, analyzed and interpreted the data, added important information to the manuscript, approved the publication; PS: as head of the clinical study group a major role in the concept and design of the study, revised the manuscript critically, and approved its publication; CAU-dG: researcher of iMTA, involved in the concept of the study, revised the article and approved its publication.

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