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Treatment Costs and Quality of Life with Granulocyte-Macrophage Colony-Stimulating Factor in Patients with Antineoplastic Therapy–Related Febrile Neutropenia

Results of a Randomised Placebo-Controlled Trial

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Summary

This study examined the costs of treatment of, and quality of life in, patients with antineoplastic therapy–induced neutropenic fever who were treated with antibacterials, with or without granulocyte-macrophage colony-stimulating factor (GM-CSF). Patients with haematological malignancies (n = 47) or solid tumours (n = 87) who had severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) and fever (>38.5°C once, or >38°C twice, in a 12-hour observation period) were randomised to receive subcutaneous GM-CSF 5 μg/kg/day (n = 65) or placebo (n = 69) in conjunction with broad-spectrum antibacterials.

GM-CSF enhanced neutrophil recovery compared with placebo. Median neutrophil counts at day 4 were 2.9 (range 0 to 25) $\times 10^9$/L in the GM-CSF arm and 1.3 (range 0 to 9) $\times 10^9$/L in the placebo group ($p < 0.001$). No significant difference was observed with regard to median days with neutrophil count $\leq 1.0 \times 10^9$/L or in time to resolution of fever.

Quality-of-life scores in 90 patients demonstrated significant differences in favour of the placebo group. The results for the oncology and haematology patients were similar to the results for the total group.

Patients in the GM-CSF and placebo groups had a mean hospital stay of 7.25 and 8.33 days, respectively. Hospital costs were higher for the GM-CSF–treated patients when GM-CSF was included in the price [mean costs: GM-CSF arm $US5177 *vs* placebo arm $US4178 ($p < 0.05$; 1992 values)]. The haematology patients stayed longer in hospital than the oncology patients, resulting in higher total costs for the former group.

These results indicate that GM-CSF does not affect the number of days required for resolution of fever or the hospitalisation period for this patient group, and does not provide a cost-effective contribution to the treatment of these patients. Sensitivity analyses indicate that GM-CSF would produce savings if the duration of hospitalisation with GM-CSF was ≤76.5% of that in the placebo group.

Febrile neutropenia is a frequent complication of antineoplastic therapy, and is associated with considerable patient morbidity and mortality.[1-3] The risk and severity of infectious complications depends on the degree and duration of granulocytopenia. Of note, the risk of serious infectious complications is generally assumed to be lower for patients with lymphomas and solid tumours than for patients with other haematological malignancies.[1,2]

Standard treatment in patients with febrile neutropenia includes hospitalisation and the administration of broad-spectrum antibacterials. In general, neutropenia lasts for 5 to 10 days after standard antineoplastic therapy.[4,5]

Haematopoietic growth factors (HGFs) are a source of interest in the treatment of febrile neutropenic patients. HGFs promote faster haematopoietic recovery by stimulating the proliferation of neutrophils, and could be administered during intensive or standard antineoplastic therapy schedules (prophylactic use), and in patients with antineoplastic therapy–related febrile neutropenia (therapeutic use).[4-9] The administration of HGFs may result in a reduction in the incidence of infections and in the severity of infectious complications.[4-9] Thus, HGFs may reduce healthcare resource utilisation, as they could reduce the risk of hospitalisation, shorten the duration of hospital stay and reduce the amount of antibacterials required.[10-12]

The pharmacoeconomic aspects of the treatment of febrile neutropenia, including HGF therapy, have been reviewed by several authors.[13,14] Those authors concluded that there is a lack of formal pharmacoeconomic analyses of HGF therapy in patients with febrile neutropenia. Furthermore, information on the possible effects of HGFs on indirect costs and quality of life is scarce.

In The Netherlands, a randomised multicentre trial has been performed to compare the effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) with those of placebo in adult patients with antineoplastic therapy–related febrile neutropenia (therapeutic use).[15] An economic evaluation was carried out in close conjunction with the clinical trial, in order to assess the costs and benefits of GM-CSF relative to placebo in such patients. In addition, we made a specific effort to monitor the quality of life of these patients.[15]

In this paper, we focus on the methodology of the economic evaluation, distinguishing between the costs of treating patients in the oncology and haematology services. Furthermore, we present the results of a sensitivity analysis. As the results of the study will be used by the Dutch Health Insurance Executive Board, we adopted a societal perspective for this economic evaluation.[16] Productivity losses, however, are not considered in this analysis, and may be assumed to be small.

Patients and Methods

Study Population

The study group comprised patients with antineoplastic therapy–related neutropenia (neutrophils $<0.5 \times 10^9$/L) and fever (temperature of >38°C twice, or >38.5°C once, over a 12-hour observation period). The patients were admitted to the haematology or oncology departments of 6 university hospitals and 1 cancer centre between September 1991 and September 1994.[15] Patients were eligible regardless of whether this was their first course of antineoplastic treatment.

Study Design

Patients were stratified according to whether they had solid tumours (treated in the oncology service) or haematological malignancies (treated in the haematological service). Subcutaneous GM-CSF (5 μg/kg/day) or placebo (both supplied by Sandoz, Basel, Switzerland) was administered once daily for between 4 and 14 days. Study treatment was started at the same time as intravenous empirical antibacterials, according to standardised local hospital policies. Both antibacterials and GM-CSF or placebo were discontinued if: (i) the patient's temperature normalised (<37.5°C); and (ii) the neutrophil count was $\geq 1.0 \times 10^9$/L for 2 consecutive days.

In the case of a neutrophil count of $\geq 10 \times 10^9$/L, GM-CSF or placebo administration was stopped, while antibacterial treatment was continued until the temperature was normalised for 2 consecutive days. The patient was then observed for a 24-hour period and, if no sign of infection was noted, the patient was discharged from the hospital. The costs and effects were analysed according to the intention-to-treat protocol. As all costs and effects were incurred in a short timespan, discounting was not applied.

Outcomes Measures

Effectiveness

The primary clinical end-point was the effect of GM-CSF on the hospitalisation period. This period was defined as the time taken for resolution of neutropenia (defined as a neutrophil count $>1.0 \times 10^9$/L) and fever (defined as a temperature <37.5°C for 2 consecutive days), followed by a 24-hour observation period.

Quality of Life

To measure effects on health status, economic evaluation requires the use of a generic (non–disease-specific) instrument for health status measurement.[17] We included the Karnofsky Performance Index and the Nottingham Health Profile (NHP).[18] The Karnofsky Index emphasises physical performance and dependency, while the NHP was selected to measure a broad spectrum of health dimensions. The following dimensions of well-being on the NHP were measured: physical mobility, emotional reactions, energy, social isolation, pain and sleep. For the general population the average score for all dimensions is less than 10 on a scale of 0 to 100, i.e. lower scores indicate better functioning.[19]

We also applied the Rotterdam Symptom Checklist,[20] a cancer-specific questionnaire that is sensitive to changes in health in patients with cancer. This questionnaire includes illness- and treatment-related items. In this study, we added questions that were related to possible adverse effects associated with GM-CSF, namely constipation, painful joints, palpitation, rash/eczema and sweating/perspiration.

In an economic evaluation, it is preferable to value health states in terms of one summary measure. Therefore, the EuroQol,[21] a valuation instrument, was included in the study. This questionnaire consists of a descriptive section and a valuation section (rating scale). A multi-attribute utility function is available to calculate the values of all health states distinguished in this questionnaire. This function can be used to arrive at utility values for each health state reported by the patients. The average EuroQol score for the general population is ≥90 on a scale of 0 to 100, i.e. higher scores indicate better functioning.[19]

Patients were asked to fill out all 4 of the questionnaires one day after stopping GM-CSF or placebo treatment. Pretreatment measurement of quality of life was not undertaken for operational reasons. Quality-of-life (QOL) items are presented as mean scores.

Costs

The cost analysis was based on a detailed review of all registry forms, daily data forms and patient files. The daily data forms included information on the type of hospital ward and consultation. Costs considered were those of in-hospital days, consultations, laboratory services, diagnostics (including imaging procedures), antibacterials

and GM-CSF. Protocol-driven costs were excluded.

For each of these activities, unit prices were determined, reflecting the real use of resources. The year of costing was 1992 [$US1 ≈ 1.8 Dutch guilders (NLG)]. The costs of hospital days were divided into variable and overhead costs. The variable costs concerned manpower (physicians, nurses, etc.) and materials (medical devices, supportive patient care, etc.) that were directly related to the treatment. The overhead costs were related to general hospital services and housing.

Patients stayed on wards that provided regular oncological care, regular haematological care, a protected environment and intensive care. The cost of hospitalisation amounted to approximately $US286 per day for regular oncological care (variable costs $US173 and overhead costs $US113). The costs for regular haematological care was approximately $US355 per day (variable costs $US239 and overhead costs $US116). Staying in a protected environment cost approximately $US551 (variable costs $US397 and overhead costs $US154) and staying on an intensive care ward cost $US1223 per day (variable costs $US974 and overhead costs $US249). Hospital costs are based on data from 2 university hospitals and 1 specific cancer centre in the Netherlands.

The output of hospital laboratories in The Netherlands is scored according to a point system. Each point can be associated with a cost price. Cost prices differ across types of laboratories. A routine test (including haemoglobin, haematocrit, leucocytes and platelets) costs $US3.58 and a bacterial culture costs about $US20.50. For the costs of diagnostics, the Dutch tariff system has been used as an approximation of unit costs (a chest x-ray costs about $US31). The drug prices used were wholesale prices. The cost of a 300μg vial of GM-CSF (parenteral) amounted to $US138 and a 400μg vial amounted to $US184.[22]

Sensitivity Analysis

An economic model, developed earlier,[23] included all relevant direct costs and savings in relation to antineoplastic therapy–induced fever and neutropenia and set out to assess the savings from a clinical application of HGFs for different patient categories. This model was applied to the patient group and used to perform a sensitivity analysis.

In the model, the relevant cost items were number of days in hospital, number of days receiving antibacterial therapy and, if applicable, the number of days receiving GM-CSF therapy. These parameters were entered into the following formula:

$$\Delta C = [(HD_1 \times HC_1) + (AD_1 \times AC_1)] - [(HD_2 \times HC_2) + (AD_2 \times AC_2) + (GMD \times GMC)].$$

where ΔC is the difference in costs (placebo minus GM-CSF), HD_1 is the number of hospital days with placebo, HD_2 is the number of hospital days with GM-CSF, HC_1 is the cost per hospital day with placebo, HC_2 is the cost per hospital day with GM-CSF, AD_1 is the number of days of antibacterial therapy with placebo, AD_2 is the number of days of antibacterial therapy with GM-CSF, AC_1 is the antibacterial cost per day with placebo, AC_2 is the antibacterial cost per day with GM-CSF; GMD is the number of days of GM-CSF therapy and GMC is the cost of GM-CSF per day.

In the model, we assumed that the hospital stay was 7.25 days in the GM-CSF group and 8.33 days in the placebo group, implying a reduction of 13% with GM-CSF. Antibacterial therapy and GM-CSF therapy were assumed to stop 1 day before hospital discharge. The mean hospital costs per day (including laboratory services, medical procedures, consultations and blood transfusions) were set at $US420 in both groups. The cost of antibacterial therapy was set at $US110 per day in both groups, and the cost of GM-CSF treatment was set at $US195 per day. This implies that: HD2 = 0.87 × HD1; AD1 = HD1 − 1; AD2 = GMD = HD2 − 1; HC1 = HC2 = 420; AC1 = AC2 = 110; and GMC = 195. This formed our baseline analysis.

Statistical Analysis

The Mann-Whitney test was used for the between-group comparisons of QOL items, neutrophil count, number of days with fever, number of

days in hospital, and the costs in each groups. A 2-sided probability level of ≤0.05 was considered to indicate statistical significance. All analyses were performed using Statistical Analysis System version 6.08 (SAS Institute, Cary, North Carolina, USA).

Results

Patient Characteristics

Of 153 patients who were randomised, 74 received GM-CSF and 79 received placebo. Nine patients in the GM-CSF group and 10 patients in the placebo group were excluded from the analysis because they did not satisfy the main entry criteria (e.g. temperature ≤38°C or granulocyte count ≥0.5 × 10^9/L). Thus, the study group consisted of 134 patients.

The patient characteristics are shown in table I. There were no statistically significant differences in the patient characteristics (age, sex and tumour type) and neutrophil count at start of the treatment. The number of days since the last antineoplastic therapy was 12 in the GM-CSF group and 13 in the placebo group.

Resolution of Neutropenia and Fever

Table II shows that the median time to recovery of the neutrophil count to ≥0.5 × 10^9/L was 3 days in the GM-CSF group and 4 days in the placebo group (difference not significant). The median time to recovery of neutrophils to ≥1.0 × 10^9/L amounted to 4 days in both groups. However, a statistically significant difference in absolute neutrophil count was observed on day 4 ($p < 0.001$). No difference was observed in time to resolution of fever; the median number of days with fever was 3 in both groups. However, the temperature curve was higher in the GM-CSF group compared with the placebo group during the first 6 days of treatment, with a significant difference at day 2 ($p < 0.05$).

Table I. Baseline characteristics of the patients studied

Characteristic	GM-CSF (n = 65)	Placebo (n = 69)
Median age (years) [range]	49 [19-73]	48 [16-70]
Number (%) of men	32 (49)	36 (52)
Number (%) of patients with:		
solid tumour	41 (63)	46 (66)
lymphoma	18 (27)	21 (30)
acute lymphoid leukaemia	6 (9)	2 (3)
Number (%) of patients with baseline neutrophil count:		
<0.1 × 10^9/L	42 (65)	39 (57)
0.1-0.5 × 10^9/L	23 (35)	30 (43)

Abbreviation: GM-CSF = granulocyte-macrophage colony-stimulating factor.

Table II. Duration of neutropenia and fever, and neutrophil count at day 4, according to treatment group. Data are shown as median (range in parentheses)

Parameter	GM-CSF (n = 65)	Placebo (n = 69)
Duration of neutrophil count (days):		
<0.5 × 10^9/L	3 (1-14)	4 (1-14)
<1.0 × 10^9/L	4 (1-14)	4 (1-14)
Neutrophil count at day 4 (× 10^9/L)	2.9* (0-25)	1.3 (0-9)
Duration of fever (days)	3 (1-14)	3 (1-14)

Abbreviation and symbol: GM-CSF = granulocyte-macrophage colony-stimulating factor; * $p < 0.005$ *vs* placebo.

Quality of Life

The results of the QOL analysis are based on the results of 90 QOL questionnaires. QOL data were missing from all participating centres, so it is very unlikely that bias would have been introduced as a consequence of this.

Table III presents the patients' QOL scores 1 day after stopping GM-CSF treatment. The Karnofsky score, and the patient score and the population score on the EuroQol, were 73, 57 and 66, respectively, in the placebo group, and 63, 55 and 54, respectively, in the GM-CSF group. The Karnofsky score and EuroQol population score were significantly higher in the placebo group than in the GM-CSF group ($p < 0.05$). According to the NHP, patients in the placebo group experienced fewer complaints concerning physical mobility, emotional problems and energy than the patients in the GM-CSF group ($p < 0.05$).

In the Rotterdam Symptom Checklist, tiredness, lack of appetite, lack of energy, dry mouth,

Table III. Mean quality-of-life scores among GM-CSF and placebo recipients for the total group, and stratified according to oncology and haematology

Instrument	Total group (n = 90)		Oncology group (n = 65)		Haematology group (n = 25)	
	GM-CSF (n = 46)	placebo (n = 44)	GM-CSF (n = 32)	placebo (n = 33)	GM-CSF (n = 14)	placebo (n = 11)
Karnofsky Index[a]	63	73*	58	72	73	75
Nottingham Health Profile[b]						
mobility	30	16**	36	15	16	17
emotional reactions	20	9**	21	11	17	4
energy	57	36*	60	36	51	36
social isolation	11	5	12	5	8	4
pain	23	19	26	19	16	18
sleep	35	24	34	22	38	32
EuroQol[a]						
patient score	55	57	56	56	55	61
population score[c]	54	66*	49	63	68	74
Most important symptoms/complaints:[d]						
fatigue	2.9	2.5	3.0	2.5	2.8	2.6
lack of appetite	2.7	2.0**	2.6	2.0	2.8	2.1
lack of energy	2.5	1.9**	2.4	1.9	2.5	1.9
dry mouth	2.4	1.9	2.5	2.1	2.1	1.7
sweating, perspiring	2.2	1.9	2.2	2.1	2.1	1.5
sore mouth/pain when swallowing	2.1	2.0	2.2	1.9	1.9	2.2

a Range 0 to 100: from worst (0) to best (100) health states.

b Range 100 to 0: from worst (100) to best (0) health states.

c Utility scores based on the valuations of patients and of a representative panel of the population.

d Answer possibilities: 1 = not at all; 2 = a little; 3 = quite a bit; and 4 = very much. The average values are presented.

Abbreviation and symbols: GM-CSF = granulocyte-macrophage colony-stimulating factor; * $p < 0.05$ *vs* GM-CSF; ** $p < 0.01$ *vs* GM-CSF.

sweating/perspiring and sore mouth/pain when swallowing represented the main problems in both groups. Problems concerning appetite and energy were less common in the placebo group ($p < 0.01$). No between-group differences were observed with regard to tiredness, dry mouth and sweating/perspiring.

The respective results for patients in the oncology and haematology services were similar to the results of the total group. In general, the Karnofsky Index, Nottingham Health Profile and the EuroQol population scores were better in the patients in the haematology services than those of the patients in the oncology services.

Costs

The average duration of hospitalisation was 7.25 days in the GM-CSF group and 8.33 days in the placebo group. Hospital care in the GM-CSF group was classified as follows: 87% regular oncological or haematological care; 11% care in a protected environment; and 2% intensive care. The hospital care of the patients treated with placebo was divided into: 86% regular oncological or haematological care; 13% care in a protected environment; and 1% intensive care.

On average, the oncology patients stayed in hospital for a shorter length of time than the patients with a haematological malignancy. The oncology patients who received GM-CSF stayed for a mean of 6.33 days in hospital, while those receiving placebo stayed 7.09 days. Haematology patients in the GM-CSF group stayed for a mean of 8.50 days in the hospital, while placebo recipients in these services stayed 9.75 days.

Table IV presents the treatment costs of patients with febrile neutropenia. The mean hospitalisation

costs amounted to $US2552 in the GM-CSF group and $US2868 in the placebo group. The cost of antibacterials was $US849 and $US786 in the GM-CSF and placebo groups, respectively. The cost of GM-CSF was $US1260. The other costs were almost equal between the 2 groups. The mean total treatment costs for the GM-CSF group were $US5177 (median $US4137; range $US1709 to $US14 650), compared with $US4178 (median $US3587; range $US1675 to $US10 987) for the placebo group ($p < 0.05$) using the Mann-Whitney test.

Table IV also shows the costs of treating oncology and haematology patients separately. Average costs were considerably higher in both haematological groups compared with both oncological groups. In the oncology services, the average costs of the patients treated with GM-CSF amounted to $US4214, while in the placebo group, these costs amounted to $US3554. In the haematology group, the mean cost for GM-CSF recipients was $US6821, compared with $US5333 for placebo recipients.

Sensitivity Analysis

Figure 1 shows the savings per patient when varying the cost per hospital day from $US280 to $US560. The hospital stay of the placebo group was varied from 5 to 15 days, and the reduction in hospital days associated with GM-CSF treatment was set at 13%. Even when the cost per hospital day was as high as $US560, a 13% reduction of the hospital stay with GM-CSF treatment did not lead to savings (fig. 1).

The reduction in duration of hospital stay, relative to the reduction with placebo, was then varied between 10 and 30% (fig. 2). When the daily

Table IV. Costs ($US; 1992 values) of GM-CSF administration in patients with febrile neutropenia (total group, and stratification for oncology and haematology)

Cost category	GM-CSF		Placebo	
	average	median (range)	average	median (range)
Total group				
Hospitalisation	2552	2131 (900-6400)	2868	2446 (1100-7100)
Antibacterials	849	630 (100-3800)	786	579 (100-2900)
GM-CSF	1260	1100 (300-3900)	0*	0*
Blood transfusions	246	149 (0-2900)	243	149 (0-2200)
Other[a]	269	253 (100-500)	281	253 (200-500)
Overall costs	**5177**	**4137 (1700-14 600)**	**4178***	**3587 (1700-11 000)***
Oncology group				
Hospitalisation	2114	2004 (900-4900)	2462	2084 (1100-6700)
Antibacterials	592	516 (0-2200)	619	487 (0-2200)
GM-CSF	1048	917 (300-2000)	0	0
Blood transfusions	202	149 (0-2300)	196	149 (0-1300)
Other[a]	258	253 (100-500)	277	253 (200-400)
Overall costs	**4214**	**4021 (1700-9100)**	**3554**	**3789 (1700-8900)**
Haematology group				
Hospitalisation	3298	3492 (1400-6400)	3629	4838 (1400-7100)
Antibacterials	1288	1000 (400-3800)	1096	1113 (200-2900)
GM-CSF	1623	1467 (300-3900)	0	0
Blood transfusions	322	149 (0-1700)	319	149 (0-2100)
Other[a]	289	259 (200-400)	288	255 (200-500)
Overall costs	**6821**	**6149 (2700-14 600)**	**5333**	**5670 (2000-11 000)**

a Including laboratory services, medical procedures and consultations.

Abbreviation and symbol: GM-CSF = granulocyte-macrophage colony-stimulating factor; * $p < 0.05$ *vs* GM-CSF.

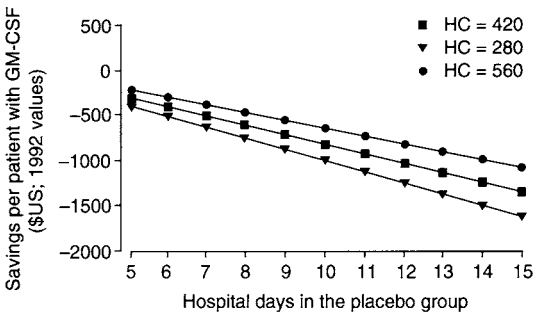

Fig. 1. Effect of varying the daily hospitalisation cost between $US280 and $US560. Reduction in hospital days in the granulocyte-macrophage colony-stimulating factor (GM-CSF) group relative to the placebo group was held constant at 13% (HD_2 = $HD_1 \times 87\%$). *Abbreviations:* HC = hospital cost per day; HD_1 = number of hospital days in the placebo group; HD_2 = number of hospital days in the GM-CSF group.

hospital cost was $US420, the break-even point was reached when the hospital stay was reduced to 76.5% of the hospital stay in the placebo group [range (90 to 70%) –$US825 to $US380]. When the daily hospital cost was as low as $US280, the break-even point was at 70.5% (range –$US940 to $US32). When the daily cost of a bed was $US560, the break-even point was at 80% (range –$US710 to $US730) [fig. 2].

Figure 3 presents the case of a break-even point of 76.5%, with regard to duration of hospitalisation (i.e. $HD_2 = 0.765 \times HD_1$). The number of days in hospital was varied from 5 to 15 days. When the hospital costs were $US420 per day and the duration of stay was longer than 8.33 days, there were no savings associated with GM-CSF; a shorter hospital stay resulted in savings with GM-CSF. When the price of a bed was $US280, there were no savings at all with GM-CSF [costs ranged from –$US670 (at 15 days) to –$US92 (at 5 days)]. Hospital costs of $US560 always resulted in savings [varying from $US235 (at 5 days) to $US315 (at 15 days)].

Discussion

Recently, 3 comparative studies of HGF in patients with neutropenia have been published.[10-12] In these studies, a significant advantage was observed for HGF treatment. Riikonen et al.[10] reported a median hospital stay of 10 days in the placebo group and 9 days in the GM-CSF group ($p < 0.05$). In the study by Maher et al.,[11] the median number of days in hospital amounted to 8 days in both groups, while the mean number of days in hospital amounted to 10 days in the antibacterial (control) group and to 8.7 days in the G-CSF group. Mayordomo et al.[12] reported that patients treated with antibacterial therapy had a median hospital stay of 8 days (range 5 to 34 days) and patients treated with antibacterial therapy in combination with either granulocyte colony-stimulating factor (G-CSF) or GM-CSF had a median hospital stay of 5 days (range 5 to 15 days) [$p < 0.05$].[12]

In our study, the mean hospital stay amounted to 8.33 days in the placebo group and to 7.25 days in the GM-CSF group (difference not significant). The differences in the number of days in hospital compared with the other studies may be explained by the fact that different patient groups were studied, and there were different rules for stopping antibacterial therapy. For example, in the studies of Riikonen et al.[10] and Maher et al.,[11] antibacterial ± HGF therapy was stopped 2 to 4 days after the patients were afebrile and the granulocyte count was $>0.5 \times 10^9$/L.[10,11] In the present study, antibacterial ± HGF therapy was stopped 1 day after

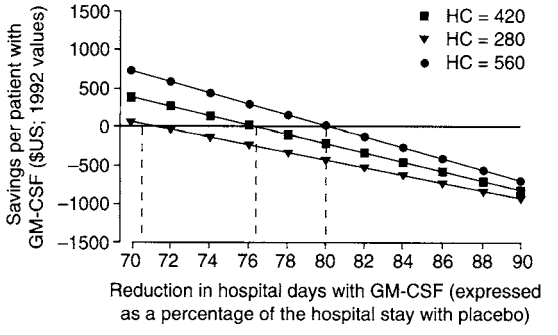

Fig. 2. Effect of varying the reduction in duration of hospital days in the granulocyte-macrophage colony-stimulating factor (GM-CSF) group, relative to that of the placebo group, for 3 different levels of daily hospitalisation costs. *Abbreviation:* HC = hospital cost per day.

the patients were afebrile and the neutrophil count was $>1.0 \times 10^9$/L.

The QOL analysis was in accordance with the toxicity analysis[15] and revealed higher scores in favour of the placebo group. The results for oncology and haematology patients were similar to those of the total group.

The costs of treating febrile neutropenia after standard antineoplastic therapy have been estimated between $US2200 and $US10 000.[4,5] In our study, the total treatment costs amounted to about $US4200 in the placebo group and about $US5200 in the GM-CSF group. The administration of HGFs adds considerably to the cost of medication. As a result, total treatment costs were significantly higher in the GM-CSF group, compared with the placebo group. Furthermore, treatment costs in both haematology groups were higher when compared with both oncology groups.

This study does not exclude a subgroup of patients (such as patients with a hospital stay of longer than 10 days) benefitting from the application of GM-CSF. In our study, the follow-up period was only 14 days and a prolonged hospital stay was only observed in 10% of the patients. This percentage makes analysis of this subgroup of patients inadequate.

The generalisability of the results may cause some problems, as our study took place in haematological intensive-care hospitals; however, such patients are also treated in regional hospitals. Treatment protocols may vary considerably between hospitals. In our study, the criteria for discharge from hospital and for stopping antibacterial regimens were well defined and, relative to other studies, the durations of hospitalisation and antibacterial therapy were very short. In regional hospitals, the duration of hospitalisation and antibacterial therapy may be longer. However, the prices of healthcare services, especially the hospital costs, will be lower in regional hospitals, compared with the centres participating in this study. By means of a sensitivity analysis, the impact of such variation on the cost effectiveness of the treatment has been demonstrated.

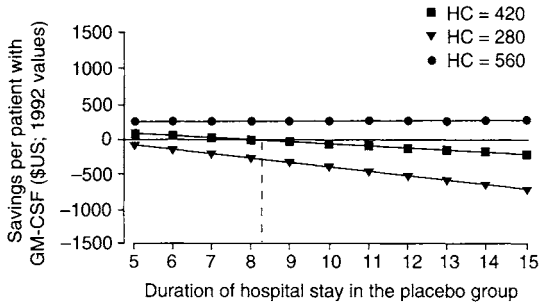

Fig. 3. Effect of varying the duration of hospital stay in the placebo group, while maintaining the relative reduction in hospital stay with granulocyte-macrophage colony-stimulating factor (GM-CSF) at 76.5% ($HD_2 = HD_1 \times 76.5\%$). *Abbreviations:* HC = hospital cost per day; HD_1 = number of hospital days in the placebo group; HD_2 = number of hospital days in the GM-CSF group.

In conclusion, the application of GM-CSF in patients with febrile neutropenia did not result in a significant shortening of the hospitalisation period, despite a faster recovery of the neutrophil count. Furthermore, the quality of life of the patients was not improved. Therefore, this intervention cannot be considered cost effective.

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