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## Original Paper

# An Economic Model to Assess the Savings From a Clinical Application of Haematopoietic Growth Factors

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**Patients receiving chemotherapy frequently develop fever and neutropenia. Haematopoietic growth factors (HGFs) may decrease the duration of such episodes or may prevent a febrile neutropenic episode. In this study we introduce a Markov type economic model for the hospital which calculates all relevant direct costs and savings of HGF therapy and may support decisons on HGF administration. A distinction is made between patients receiving intensive and standard chemotherapy schedules. Our results indicate that HGFs can induce savings in intensive chemotherapy and standard chemotherapy following neutropenic fever. Prophylactic administration of HGF is cost-effective if the risk of infection is considerable. The risk of infection depends on underlying malignancy, corresponding treatment modalities and the health condition of the patient. The model is meant as an analytical framework and should be used carefully, as not all benefits (e.g. benefits to the patients) are considered. These benefits may be balanced against the additional costs or savings resulting from the economic model.**

**Key words: costs, fever, neutropenia, chemotherapy, sensitivity analysis, Markov model**
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## INTRODUCTION

NEUTROPENIA IS closely related with the treatment of cancer. The risk of a life-threatening infection increases significantly when the neutrophil count falls below $0.5 \times 10^9$/l and is a major cause of death in cancer patients. Furthermore, the duration of neutropenia has an important role in the design, schedule, and dose of cancer treatment regimens [1, 2]. Treatment-related neutropenia is highly variable, ranging from days to weeks.

Neutropenic patients with fever require prompt initiation of early broad spectrum antibiotic therapy. Moreover, haematopoietic growth factors (HGFs), such as granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF), are becoming increasingly important in the treatment of febrile neutropenic patients [3, 4]. HGFs are indicated for rapid haematopoietic reconstitution by stimulating the proliferation of neutrophils, and could be administered during intensive chemotherapy schedules, during standard chemotherapy cycles and in patients with chemotherapy-induced fever and neutropenia [5–8].

The administration of HGFs during intensive chemotherapy regimens mainly concerns patients undergoing autologous bone marrow transplantation (ABMT) or peripheral blood progenitor cell (PBPC) transplantation and patients with acute myeloid leukaemia (AML). These patients remain neutropenic for 3–4 weeks [8–10]. They are all hospitalised and treated with broad spectrum antibiotics. HGF therapy may reduce the period of neutropenia and may result in shortening of the period of hospitalisation and antibiotic therapy.

Prophylactic administration of HGF during and after standard chemotherapy cycles is already applied in patients with small cell lung cancer [6, 7, 11]. The standard chemotherapy is mainly given on an outpatient basis. When patients become febrile and neutropenic during a given cycle of treatment, they are generally hospitalised and receive standard parenteral antibiotic agents [4, 8, 12, 13].

At a time of restrained public spending, hospitals are coming under increasing pressure to deliver more services with less resources. The main cause of rising hospital drug expenditure in leading Western European countries are antibiotics [14]. The administration of HGFs may lead to less infections and as a result to less antibiotic administrations. Furthermore, it could result in a lower risk of hospitalisation and a shorter stay in hospital. Thus, the use of HGFs may decrease utilisation of some health care resources [15]. Glaspy and colleagues developed an economic model to demonstrate the savings of prophylactic administration of the haematopoietic growth factor G-CSF (filgrastim) in patients with small cell lung cancer. The analysis was conducted in conjunction with a phase III clinical trial [6]. The data were derived from three of the 14 hospitals included in

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the clinical trial. However, the clinical results in these three hospitals differed from the results of the total study. For example, in the larger trial, the number of days in hospital and the number of days with antibiotic therapy were similar in both groups once patients were hospitalised, while in the economic model not only did the number of hospitalisations decrease by almost 50%, but the duration of hospital stay also decreased by almost 50%. Furthermore, Glaspy's study focused on the administration of haematopoietic growth factors in one patient group.

The aim of this study is to develop an economic model for the hospital, which includes all relevant direct costs and savings in relation to chemotherapy-induced fever and neutropenia. Three categories of treatment choices will be presented: the first category considers a treatment option where HGFs are administered during intensive chemotherapy cycles. The second category describes a prophylactic option where HGFs are administered during and after standard chemotherapy cycles, which are given on an outpatient basis. When the patients become febrile and neutropenic, they are hospitalised and treated with broad spectrum antibiotics. The aim of HGF administration in this second category is to prevent patients from developing fever and neutropenia. It may be applied during the first chemotherapy cycle or during consequent cycles.

The third category concerns a treatment option in, for example, solid tumour patients and patients with non-Hodgkin's lymphoma. These patients receive standard chemotherapy cycles again on an outpatient basis and subsequently may develop fever and neutropenia. The purpose of administering antibiotics in combination with HGFs is to shorten the period of fever and neutropenia.

The model is meant for hospital pharmacists, doctors and hospital management. The perspective of the study is that of the hospital and, therefore, only the direct costs of outpatient and inpatient treatment are considered.

## MATERIALS AND METHODS

*Development of the model*

The costs of the treatment alternatives will be compared by subtracting the estimated total costs used for the group treated with conventional therapy from the estimated total costs for the group treated with HGF therapy. For all categories, the following formula is used to calculate the cost or benefit of the HGF therapy:

$$\Delta C = \Sigma C_1 - \Sigma C_2,$$

where $\Delta C$ = differential treatment cost, $\Sigma C_1$ = total treatment costs of conventional therapy without HGF and $\Sigma C_2$ = total treatment costs of HGF therapy.

This formula implies that if $\Delta C$ is positive, the conventional therapy is more expensive than HGF therapy. The situation with $\Delta C = 0$ marks the break-even point and if $\Delta C < 0$ then the administration of HGFs does not lead to savings.

Figure 1 shows the three categories in the hospital economic model. In category I, all patients are treated with intensive chemotherapy and stay in hospital for a few weeks. During and after the administration of cytostatics, they are treated either with antibiotics or with antibiotics in combination with HGF therapy. The relevant cost items are days in hospital, days with antibiotics and, if applicable, the number of days with HGF. This results in the following formula:

$$\Delta C_I = \{(HD_{I1} \times HC_I) + (AD_{I1} \times AC_I)\} - \{(HD_{I2} \times HC_I) + (AD_{I2} \times AC_I) + (HGFD_I \times HGFC)\},$$

where $\Delta C_I$ = differential costs in category I, $HD_I$ = number of hospital days, $HC_I$ = cost per hospital day, $AD_I$ = number of days with antibiotic therapy, AC = antibiotic cost per day, $HGFD_I$ = number of days with HGF therapy and HGFC = cost of HGF per day.

Category II concerns patients who receive standard chemotherapy. These patients may be treated with HGF on a prophylactic basis. This means that all patients receive HGF directly after completing their chemotherapy. When the HGF is not applied, the so-called "wait and see" option, there is a probability that fever and neutropenia develop $P(FN1)$. Once this event has set in, antibiotics or antibiotics plus HGFs are administered (category III). Delay of administration of the following chemotherapy cycle may occur, resulting in extra outpatient visits. The relevant cost items are days in hospital, days with antibiotics and number of extra outpatient visits. For this category the following formula applies:

$$\Delta C_{II} = \{P(FN1) \times ((HD_{II1} \times HC_{II}) + (AD_{III} + AC_{II}) + (P(EO_{II1}) \times EO_{II1} \times OC_{II}))\} - \{(P(FN2) \times ((HD_{II2} \times HC_{II}) + (AD_{II2} \times AC_{II}) + (P(EO_{II2}) \times EO_{II2} \times OC_{II}))) + (HGFD_{II} \times HGFC)\},$$

where $\Delta C_{II}$ = differential costs in category II, $P(FN)$ = probability to develop fever and neutropenia, $HD_{II}$ = number of hospital days, $HC_{II}$ = cost per hospital day, $AD_{II}$ = number of days with antibiotic therapy, $AC_{II}$ = antibiotic cost per day, $P(EO_{II})$ = probability of extra outpatient visits, $EO_{II}$ = average number of extra outpatient visits, $OC_{II}$ = cost of an outpatient visit, $HGFD_{II}$ = number of days with HGF therapy and HGFC = cost of HGF per day.

Category III handles patients who develop fever and neutropenia due to standard chemotherapy. The chemotherapy is administered on an outpatient basis, but the patients are hospitalised for their fever and neutropenia. Delay of chemotherapy administration may happen in both groups. The formula is the same formula as for category I.

Default values of the probability to develop fever and neutropenia, the hospitalisation risk, the number of days in hospital, the cost of an outpatient visit, the number of days with antibiotics and the number of days with a HGF are based on literature review. Cost prices are derived from previous Dutch studies on the cost-effectiveness of cancer treatment in the relevant patient groups [10, 16]. Sensitivity analyses are carried out to provide insight into the effect of changes in the probability to develop fever and neutropenia, days in hospital and cost per hospital day on the total treatment costs.

We specified a Markov model to estimate the consequences of HGF administration when more (standard) chemotherapy cycles are given and possible combinations of category II and III are considered. Patients treated with antibiotics or HGF therapy in the previous cycle are assumed to receive the same treatment in the following cycles.

We used the computer programme Quattro Pro for Windows.

*Default values*

*Category I.* In the study of Nemunaitis and colleagues [17], the median duration of the initial hospital stay was 27 days in the HGF group as compared to 33 days in the placebo group. This is a reduction of 20% and is consistent with results reported

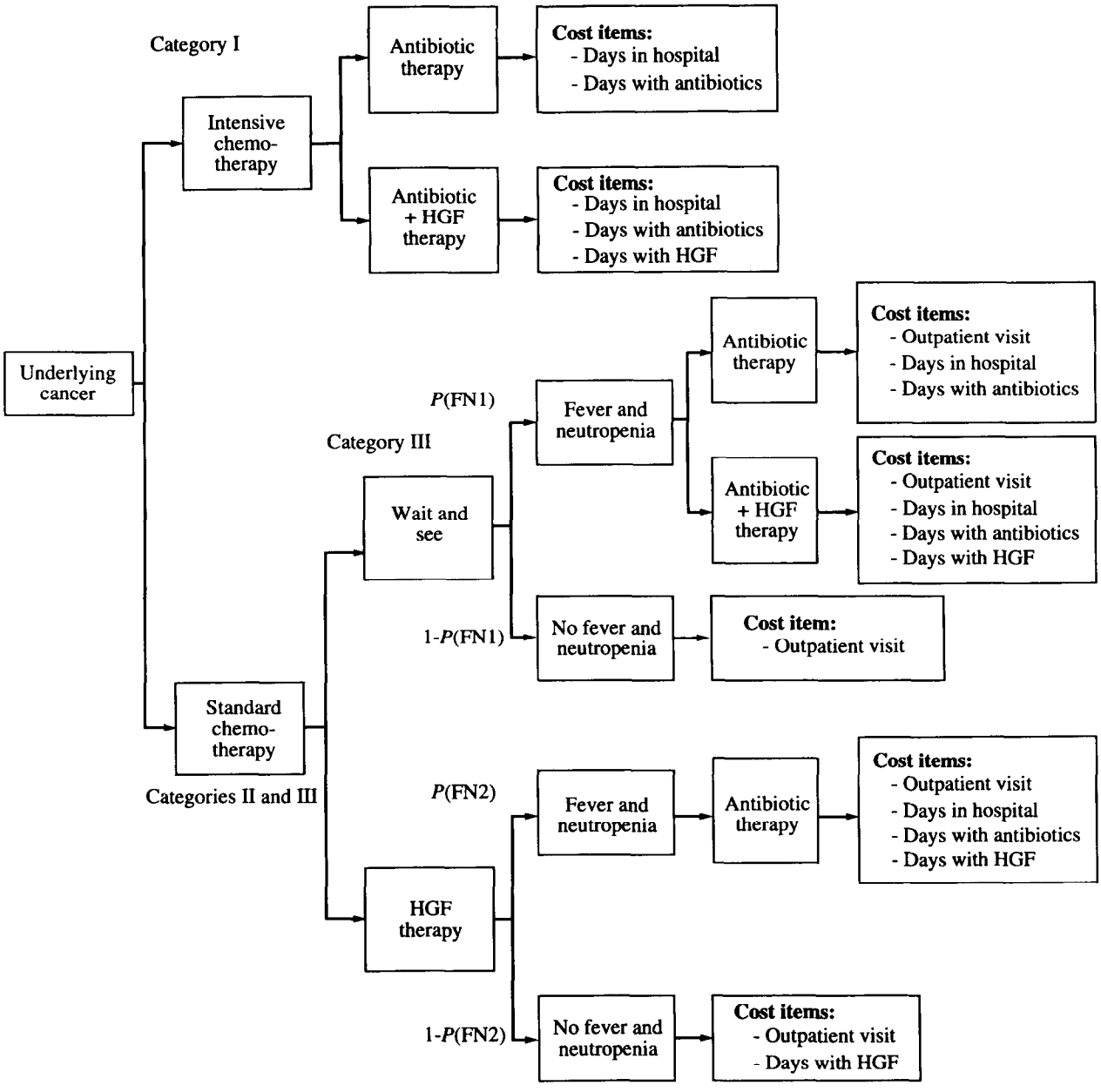


**Figure 1. Hospital economic model.**

elsewhere [18]. The number of days with antibiotics was approximately 82% of the days in hospital in the placebo group. This percentage was 89% in the HGF group. For the formula, this implies that: $HD_{I2} = 0.8 \times HD_{I1}$, $AD_{I1} = 0.82 \times HD_{I1}$ and $AD_{I2} = 0.89 \times HD_{I2}$.

*Category II.* In category II, the conventional therapy is the "wait and see" option. Patients only receive antibiotics when they develop fever and neutropenia. The default values will be similar as in category III. The other option is that all patients receive HGF therapy. HGFs are given for, on average, 10 days (range 7–14) [6, 7, 19]. Crawford and associates and Bronchud and associates reported a reduction of the event rate for fever and neutropenia by 50% in the HGF group as compared with the "wait and see" option [6, 7]. The average duration of the individual episodes of antibiotic use and hospital stay in case of fever and neutropenia, were similar in both treatment groups.

In the study by Gerhartz and associates, the event rate decreased by 40% [19]. The reduction in infection distributed equally through all six cycles of chemotherapy. Patients receiving HGF had shorter stays in hospital than the patients treated with placebo. The percentage of chemotherapy cycles finished on time was 54% in the HGF group and 34% in the placebo group. However, data on the average number of delayed chemotherapy schedules per patient were not shown. To simplify the models, these probabilities are set to zero. The assumptions made are $P(FN2) = 0.5 \times P(FN1)$, $HGFD_{II} = 10$ and once the event has set in: $HD_{III} = HD_{II2}$, $AD_{III} = AD_{II2}$ and $P(EO_{III}) = P(EO_{II2}) = 0$.

*Category III.* In the study by Mayordomo and associates [20], patients treated with antibiotic therapy had a median hospital stay of 8 days (range 5–34) and patients treated with antibiotic therapy in combination with HGF had a median hospital stay of 5 days (range 5–15) [20]. This implies a reduction of 37% in hospital days. In the study by Maher and associates [21], 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 antibiotic group and to 8.7 days in the HGF group. The difference in hospital stay between the studies of Mayordomo and Maher could be explained by differences in definition of fever and neutropenia and differences in doses of HGF administration. In the model, we assume that the hospital stay is 10 days in the antibiotic group and 8 days in the antibiotics with HGF group, implying a reduction of 20%. The antibiotic therapies consisted of piperacillin and tobramycin, ceftazidime and amikacin or tobramycin and cefuroxime [5,19,20]. The antibiotic therapy and/or HGF therapy was stopped approximately 2 days before hospital discharge. This implies that: $HD_{III2} = 0.8 \times HD_{III1}$, $AD_{III1} = (HD_{III1} - 2)$ and $AD_{III2} = HGFD_{III} = (HD_{III2} - 2)$.

For the Markov model, all default values were applied. Data on patients developing FN in subsequent cycles were not available. According to interviews with clinical experts, we made the assumption that patients with a previous FN have a 95% change of FN in the next cycle and that patients with no previous FN have a 5% chance of FN in the next cycle.

*Unit prices*

In the Netherlands, the cost of hospitalisation amounts to approximately US$350 per day for normal haematological care, to approximately US$536 per day for a stay in a protected environment and to about US$1223 per day for a stay on an intensive care ward [10, 16]. These costs do not include the costs for laboratory services and medical procedures. The laboratory services mainly consist of routine haematological laboratory services and cultures. The medical procedures include X-rays and ECGs. We estimate these costs at US$50 per hospital day.

The patients who receive intensive chemotherapy stay more frequently and longer in a protected environment and/or on an intensive care ward. Furthermore, in The Netherlands, these patients are treated in haemato-intensive care hospitals, thus the hospital costs are in this case higher than in the standard chemotherapy strategies. We use US$600 as an estimation for the average cost of a day in hospital for the patients receiving intensive chemotherapy schedules. The costs for laboratory services and medical procedures are included in this price. For the patients who receive standard chemotherapy, we estimated a cost price of US$450 for a hospital day in a regional hospital. The costs of antibiotic therapy are estimated at US$100 per day. The recommended amount of HGF varied from 3.5 to 12 $\mu$g/kg day. In the model, we use a unit price of US$138, that is the cost of a 300-$\mu$g vial of G-CSF or GM-CSF.

## RESULTS

*Category I: group receiving intensive chemotherapy*

The results of the costs of conventional antibiotic treatment and antibiotic plus HGF therapy are summarised in Table 1. Antibiotic therapy costs are about US$22 510 and the antibiotic plus HGF therapy cost about US$21 550. The model suggests that antibiotic plus HGF therapy results in a saving of US$960 in comparison with a therapy with antibiotics alone.

In Figure 2, the number of days in hospital when no HGF is given ($HD_{II}$) ranged from 25 to 40 days. The model shows that the level of savings varies from US$28 ($HD_{II}$ = 25 days) to US$1780 ($HD_{II}$ = 40 days) (Figure 2). For this range, the conventional therapy is more expensive than the antibiotics plus HGF therapy.

Sensitivity analyses were performed to assess the effect of changes in the number of days in hospital and the cost per hospital day. The cost per hospital day ranged from US$400 to US$800. When the hospital cost is lower than the default value of US$600, the savings obviously decrease. For example, when the hospital cost is US$400, the savings range from US$−870 ($HD_{II}$ = 25 days) to US$340 ($HD_{II}$ = 40 days). The break-even point, i.e. no cost difference between the two treatment groups, is at 35.8 days. When the hospital costs are higher than the default value, for example US$800, the savings are higher and range from US$930 ($HD_{II}$ = 25 days) to US$3220 ($HD_{II}$ = 40 days).

When the number of days in hospitals decreases by a smaller percentage, due to HGF therapy, than the default value of 20% reduction, the savings are smaller.

*Category II: group receiving standard chemotherapy ± prophylactic HGF therapy*

The costs of fever and neutropenia treatment with and without a HGF depend on the probability of developing fever and neutropenia ($P$(FN)). The chance of savings increases with the risk of fever and neutropenia. A relatively small risk of fever and neutropenia results in ineffective HGF administration in many patients and leads to additional net costs. Taking into account the default values and a $P$(FN1) of 57% [6], there will be a saving with the HGF therapy of US$130 (Table 1).

A sensitivity analysis was performed to assess the impact of varying the risk of developing fever and neutropenia from 0 to 100% (Figure 3). When the hospital cost is US$450, the savings ranged from US$−1380 to US$1470. The break-even point is at 52%, implying that below this level the HGF strategy is more expensive than the conventional antibiotic treatment.

Furthermore, we varied the price of a hospital day by US$150. The *a priori* chance of $P$(FN2) still is 0.5 × $P$(FN1). When the hospital cost is as low as US$300, the savings range from US$−1380 to US$520. The break-even point is at approximately 72.7%. If the price of a bed day is US$600, the savings range from US$−1380 to US$2220 and the break-even point is at 38.4%.

When $P$(FN2) decreases to less than 50% of $P$(FN1), the savings are smaller. A more than 50% reduction of $P$(FN2) results in more savings.

*Category III: group receiving standard chemotherapy and developing fever and neutropenia*

In this group, the average duration of the hospitalisation period is shorter than in the group receiving intensive chemotherapy. Furthermore, the cost per day in hospital will be lower. Taking into account the default values, the costs in the antibiotic group amount to US$5300 and in the HGF group US$5028 (Table 1). This results in a saving of US$272 in favour of the HGF therapy. Figure 4 shows that, in this case, the outcomes are not very sensitive to changes in the number of days in hospital. The savings range from US$274 to 270.

When the hospital cost amounts to US$300, the savings range from US$124 ($HD_{I}$ = 5 days) to US$−180 ($HD_{I}$ = 15 days). The break-even point is at 9.0 days. Hospital cost of US$600 per day always result in savings (range: US$424 – 720).

*Markov model*

Considering category III over three chemotherapy cycles and the default values, the cumulative costs amount to US$8955 in the conventional antibiotic therapy group. When HGF is used as treatment option in case of fever and neutropenia, the cost

*Table 1. Costs of conventional and HGF therapy per category (in US$)*

| Categories | Costs of antibiotic therapy | Costs of antibiotic + HGF therapy | Cost difference |
|---|---|---|---|
| Category I (intensive chemotherapy group) | | | |
| Hospital costs | 19800 | 16240 | 3560 |
| Costs of antibiotics | 2710 | 2410 | 300 |
| Costs of HGFs | — | 2900 | −2900 |
| Total costs | 22510 | 21550 | 960 |
| Category II (standard chemotherapy group) | | | |
| Hospital costs | 2565 | 1280 | 1285 |
| Costs of antibiotics | 455 | 230 | 225 |
| Costs of HGFs | — | 1380 | −1380 |
| Total costs | 3020 | 2890 | 130 |
| Category III (standard chemotherapy group) | | | |
| Hospital costs | 4500 | 3600 | 900 |
| Costs of antibiotics | 800 | 600 | 200 |
| Costs of HGFs | — | 828 | −828 |
| Total costs | 5300 | 5028 | 272 |

Assumptions: P(FN1) = 57%; $HD_{II,III}$ = 10; default values. HGF, haematopoietic growth factor.

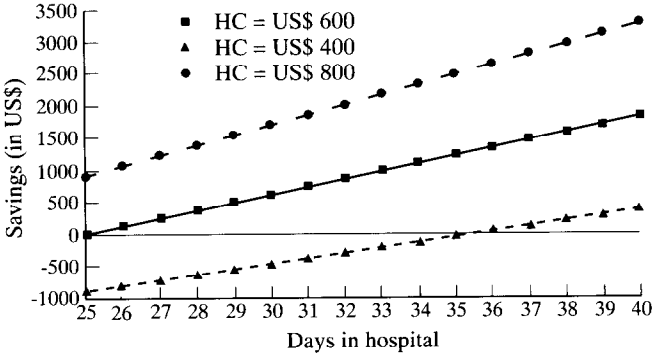


**Figure 2. Group receiving intensive chemotherapy (category I).**

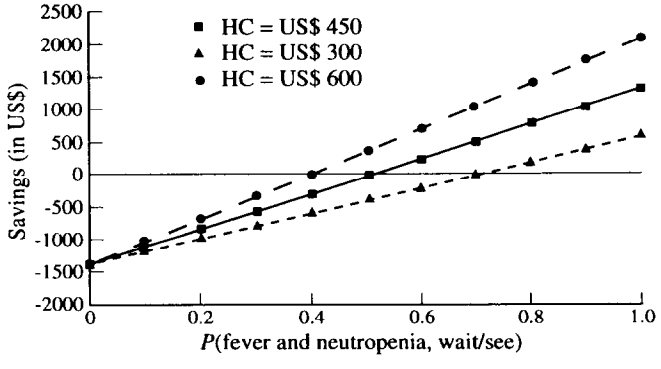


**Figure 3. Group receiving standard chemotherapy (category II).**

amounts to US$8496. Prophylactic use of HGF over three cycles results in a cost of US$9002. This implies that HGF as a treatment option in fever and neutropenic patients produces the lowest costs. However, this option is accompanied by having fever and neutropenia and its associated risks of (fatal) complications. Furthermore, it could result in dose reduction and delay of chemotherapy administration. The latter frequently requires extra outpatient visits. In The Netherlands, an outpatient visit

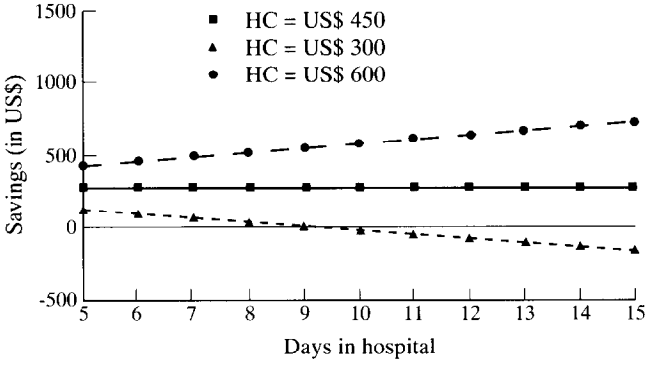


**Figure 4. Group receiving standard chemotherapy (category III).**

costs approximately US$90 [10]. Assuming that one delay of chemotherapy administration requires one extra outpatient visit, it already implies that a 50% delay of chemotherapy administration results in equal costs in the prophylactic strategy and the "wait and see" strategy with conventional antibiotic treatment.

Another option is to give HGF only prophylactically when patients have previously had fever and neutropenia. The patients receive HGF plus antibiotic therapy for their first febrile neutropenic episode. We assumed that the probability of fever and neutropenia in the next cycle will be reduced by 50%. Fever and neutropenia after prophylactic HGF therapy will be treated with antibiotics. Taking into account the default values and a *P*(FN1) of 57%, the cumulative costs of this option amount to US$7975.

A sensitivity analysis demonstrates the effect of changing the probability of developing fever and neutropenia. Figure 5 shows that when the probability of fever and neutropenia is lower than 80%, prophylactic administration of HGF to patients who have had previous fever and neutropenia produces the lowest cost. Probabilities above 80% favour prophylactic HGF therapy during all cycles.

## DISCUSSION

The administration of HGF is adding considerably to the cost of medication [22], but this hospital economic model indicates

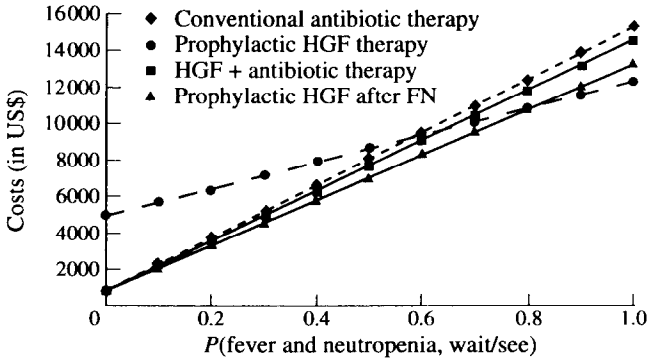


**Figure 5. Groups receiving three cycles of standard chemotherapy (Markov).**

that the administration of HGF may lead to savings in daily hospital practice. In the intensive chemotherapy and the "wait and see" option, HGF is cost-effective for almost all basic assumptions. However, standard chemotherapy is often administered in regional hospitals, where the cost of a hospital day is lower than in haemato-intensive care hospitals. When patients stay longer than 9.0 days in hospital and/or the hospital costs are below US$300, the HGF administration does not result in savings.

The prophylactic administration of HGF, whether or not there are savings, largely depends on the probability of developing fever and neutropenia. This probability differs between underlying malignancies, corresponding treatment modalities and the health condition of the patients. In our model, the administration of HGFs in patients with a high risk of infections leads to savings. This suggests that it is worthwhile identifying other determinants of high risks of infections, such as patient history (infection at previous cycles) or other patient or hospital specific factors thought to influence the risk of infection.

This hospital economic model is meant as an analytical framework to assess the savings from clinical application of HGFs. It is applicable to any hospital in any country, regardless of practice patterns, since hospital and/or country-specific data can be used. It may support decision-making about the treatment of certain patient groups as well as negotiating budget transfers with hospital management. It only requires a few relatively simple data from the hospital accounting system and the medical registration system. One of the available spreadsheet programmes may be used to calculate quickly the differential costs, given hospital- and patient-characteristic data.

However, the model should be used carefully, as the benefits to the patients, such as improved quality of life as a result of shorter stay in hospital and less infections, are not considered. Other benefits may be less delay of chemotherapy administration, less distress to the patient and less travel costs. There may also be indirect savings (decreased loss of productivity). These benefits may be balanced against the additional costs (or added to the savings) resulting from the economic model.

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