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A novel approach to maintain planned dose chemotherapy on time: a decision-making tool to improve patient care

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Abstract

Studies of primary prophylaxis of febrile neutropenia with recombinant granulocyte colony-stimulating factor (r-metHuG-CSF, filgrastim), administered to all patients starting with the initial course of chemotherapy, have demonstrated an economic advantage over a wide range of settings. In these analyses, the threshold risk for febrile neutropenia at which a cost saving is realised is inversely related to the direct medical costs of hospitalisation. Clinical practice guidelines for the use of filgrastim have been developed based on these observations. Recent studies incorporating indirect institutional costs have demonstrated that cost savings can be achieved at substantially lower febrile neutropenia risk thresholds than previously estimated. Despite the demonstrated efficacy of filgrastim in primary prophylaxis, its value may be further enhanced through the appropriate selection of patients for such therapy and a better understanding of the importance of sustaining dose intensity in specific malignancies. Clinical prediction models capable of identifying individuals at high risk for neutropenic complications yield further reductions in febrile neutropenia risk thresholds and treatment costs in patients receiving cancer chemotherapy. Prediction models can also be used to evaluate the cost-effectiveness or cost-efficiency of filgrastim use. Such a model has recently been developed and validated and is described here which incorporates both baseline clinical characteristics as well as the results of the first cycle of chemotherapy in patients with early-stage breast cancer. A cost-effectiveness ratio of US$ 34 297 (Euro 32 002)† per year of life saved (YLS) was calculated based on dose–response assumptions derived from a previously reported adjuvant breast cancer trial studying the impact of dose reduction on disease-free survival. This figure is comparable with accepted cost-effectiveness ratios for other interventions, e.g. US$ 45 000/LYS (Euro 41 989) for renal dialysis for patients with end-stage renal disease. The cost-effectiveness of filgrastim was evident over a wide range of clinical and cost assumptions. Clinical prediction models permit rational and cost-effective selection of patients for filgrastim support. Current guidelines should be re-evaluated in light of new information available on both the total cost of febrile neutropenia, as well as the cost-effectiveness of these agents in specific clinical situations.

Keywords: Febrile neutropenia; Cost-minimisation; Cost-effectiveness; Filgrastim; Clinical prediction models

1. Introduction

Febrile neutropenia and its complications are the major dose-limiting toxicities in patients receiving systemic cancer chemotherapy. Recombinant granulocyte colony-stimulating factor (r-metHuG-CSF, filgrastim) has been shown to reduce the severity and duration of neutropenia in this setting [1,2]. Trials conducted in both Europe and the USA have demonstrated the ability of filgrastim, when administered prophylactically, to reduce the risk of febrile neutropenia in patients receiving systemic chemotherapy [3,4]. The decision to use filgrastim should consider both the clinical efficacy as well as the costs of growth factor and any hospitalisation for febrile neutropenia. In this review, data will be summarised that demonstrate the cost savings associated with filgrastim prophylaxis in cancer chemotherapy. The cost-effectiveness of filgrastim treatment in patients with early-stage breast cancer based on a clinical prediction model will also be discussed.

2. Healthcare costs and economic analyses

The global costs of healthcare, including that for cancer care, are considerable and continue to rise in most countries. More than US$100 billion is spent

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† An exchange rate of US$ 1 equivalent to Euro 1.0717 was used in this paper (30 March 1999).

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annually on cancer care at the present time in the USA alone [5]. Hospital care is the largest single component of this expenditure, accounting for approximately 40–50% of the total. This is followed by physician services (23%), home healthcare (12%) and other professional services (11%), whilst drug expenditure accounts for approximately 10%. Types of healthcare costs include direct medical and non-medical costs at the time of treatment, indirect costs in between treatments and intangible costs such as pain and suffering.

Given the very high expenditure for cancer care, economic analyses evaluating costs alongside traditional measures of healthcare outcome have gained increasing importance. Economic analyses attempt to study the trade-off between these costs and the benefits of specific interventions. Common measures of clinical efficacy in an economic analysis include life expectancy, which is the average number of years of life remaining at a given age (life years), or the quality-adjusted life year (QALY). Economic outcomes of interest in economic analyses generally consist of costs or the ratio of costs and benefits in the form of cost-effectiveness or cost-utility ratios expressed as the cost per life year or QALY gained. Economic analyses have been found to be particularly useful in evaluating new and often costly healthcare technologies in the setting of limited resources. Such analyses are critical to rational clinical and public health decision making. They have placed health technology assessment and the development of clinical practice guidelines on a more rational basis. These analyses are of greatest importance in two settings: (a) if the outcome of treatment is the same or better but the costs are higher; or (b) if the costs are the same or less but the outcome is not as good. Types of economic analyses include cost minimisation, cost-effectiveness and cost-utility studies. Filgrastim has been the subject of a number of economic analyses in recent years [6–8].

3. Efficacy of filgrastim

The colony-stimulating factors (CSFs) act on early cells in the haematopoietic system to produce morphologically and functionally mature cells. Filgrastim is a bacterially synthesised recombinant form of the human granulocyte colony-stimulating factor (G-CSF). It acts specifically on neutrophils, the body's major defence against bacterial infection. The original randomised clinical trials in both Europe and the USA demonstrated a significant reduction in the risk of febrile neutropenia, helping to establish the efficacy of filgrastim as an adjunct to myelosuppressive chemotherapy [3,4].

Crawford and colleagues randomised patients with small-cell lung cancer in a prospective, double-blind, placebo-controlled trial of filgrastim following treatment with cyclophosphamide, doxorubicin and etoposide (CAE) [3]. During the first cycle of treatment, when all patients were in the double-blinded portion of the trial, 27% of filgrastim patients experienced febrile neutropenia compared with 55% of placebo control patients ($P < 0.001$). One or more episodes of febrile neutropenia occurred in 77% of the placebo group over the six possible treatment cycles compared with 40% of the filgrastim group ($P < 0.001$).

In a nearly identical trial performed by Trillet-Lenoir and colleagues, patients with small-cell lung cancer were also randomised to treatment with CAE with or without filgrastim [4]. Although the risk of febrile neutropenia was less in both groups, the overall treatment effect was similar to the Crawford Study. Over all courses of chemotherapy, 53% of the placebo patients and 26% of the filgrastim patients experienced at least one episode of febrile neutropenia ($P < 0.001$). Importantly, significant decreases in the need for treatment delay (47 versus 29%, $P < 0.04$) or dose reduction (61 versus 29%, $P < 0.001$) were observed in filgrastim patients.

4. Previous economic analysis

Filgrastim has been the subject of a number of economic analyses comparing filgrastim treatment options based on differences in resource utilisation or cost [6–9].

Lyman and colleagues conducted a cost-minimisation analysis based on a clinical decision model requiring specification of the clinical decision, the probabilities of various events and the associated costs [6,7]. The fundamental clinical question was whether or not to add filgrastim as primary prophylaxis following chemotherapy. There is a certain probability of febrile neutropenia with each treatment option. Baseline probabilities were derived from the Crawford trial and included a 50% reduction in the risk of febrile neutropenia in filgrastim-treated patients. The costs of managing or preventing febrile neutropenia considered in the analysis were derived from local institutional sources and included the direct medical costs of filgrastim and/or hospitalisation for febrile neutropenia. Sensitivity analysis demonstrated that the total cost of treatment rises in both groups as the probability of febrile neutropenia increases, but the cost increases more rapidly in patients who do not receive filgrastim. A threshold risk for febrile neutropenia of 40% was estimated at which the added cost of filgrastim was balanced by the reduction in cost associated with hospitalisation for febrile neutropenia. Above this risk threshold, the overall costs of treatment are less when filgrastim is used, whilst below it the use of filgrastim increases the costs of treatment. Similar thresholds were generated in other studies and eventually incorporated into clinical

guidelines for filgrastim treatment [10,11]. A two-way sensitivity analysis is shown in Fig. 1 defining a threshold curve where hospital cost and risk result in equal costs with and without filgrastim. Any combination of hospital cost and risk of febrile neutropenia falling above the curve is associated with a lower cost of care with filgrastim use, whilst below the curve the use of filgrastim increases costs. Clinical practice guidelines for the use of haematopoietic growth factors have been developed based, in part, on these analyses [10,11].

The major economic factor driving costs in these studies was that associated with hospitalisation for febrile neutropenia. Any consideration that increases the cost of treating febrile neutropenia, including hospitalisation costs, will decrease the risk threshold and favour the use of filgrastim. A recently updated analysis has added indirect institutional costs of care for patients with febrile neutropenia to the direct costs previously reported, raising the average total cost of hospitalisation to the range of US$1600 to US$1800 per day and reducing the febrile neutropenia risk threshold to nearly 20% [12] (Fig. 1). Similar considerations apply to the duration of hospitalisation for febrile neutropenia. The recent analysis identified a group of patients who experienced considerably greater lengths of hospitalisation for febrile neutropenia. As the lengths of stay and, therefore, the total cost of hospitalisation increase, the threshold risk based on the cost model decreases, falling below 20% in patients with complicated episodes of febrile neutropenia. Therefore, where hospital costs are high, as in the USA and parts of Europe, or where a long hospitalisation is anticipated, primary prophylaxis with filgrastim will reduce the total cost of care when the risk of febrile neutropenia is approximately 20% or greater. Primary prophylaxis with filgrastim should, therefore, be based not only on the risk of febrile neutropenia but also on the costs of hospitalisation and the anticipated length of stay.

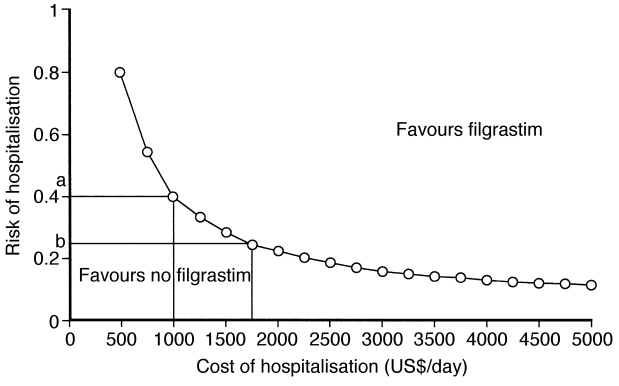

Fig. 1. Cost-minimisation analysis with filgrastim in primary prophylaxis. Two-way sensitivity analysis indicating the threshold curve for treatment with filgrastim [12]. If a combination of costs or risk of hospitalisation puts a patient above the curve then the use of filgrastim is cost saving. Below the threshold curve the benefits of using filgrastim are offset by its added cost. [a]Current national guideline, based on [6]. [b]Based on revised cost estimates [12].

In recent years there has been a move towards decreasing costs and improving patients' quality of life by attempting to treat 'low-risk' febrile neutropenia with oral or intravenous (i.v.) antibiotics administered on an outpatient basis [13]. The factors that have been used to identify low risk in clinically stable patients include a short duration of neutropenia, solid tumours and the absence of a low absolute neutrophil count [14,15]. This approach may reduce the hospital costs of treating low-risk patients with febrile neutropenia. However, the costs of inpatient care for the higher-risk patients requiring longer hospitalisations will remain high. Clearly, there is a need for randomised clinical trials to support the widespread application of outpatient treatment for low-risk febrile neutropenia [16].

5. Clinical prediction models

Clinical prediction models can increase the power of an economic analysis and reflect more closely the situation seen in actual clinical practice, where patients are selected for treatment based on certain predictive criteria. Clinical prediction models may allow patients to be divided into high- and low-risk categories for neutropenic complications and filgrastim may be selectively applied to the high-risk group. This approach can improve the efficiency of resource allocation by permitting patients who benefit most to receive the appropriate treatment. Clinical prediction models have both dependent (or outcome) variables and independent (or predictive) variables. The outcome measures of economic analyses based on clinical prediction models include the impact on cost (cost-minimisation) or the simultaneous impact on cost and treatment effect (cost-effectiveness). Clinical prediction models can be based on either pretreatment characteristics alone (unconditional) or also include the response to initial treatment (conditional).

A simple clinical prediction model utilised frequently by treating clinicians is to administer filgrastim to patients who have previously experienced an episode of febrile neutropenia. Such patients are considered to be at increased risk for subsequent neutropenic complications. The power of a predictive model based on such experience can be illustrated by reference to a recent study of febrile neutropenia in patients with small cell lung cancer [17]. Eighteen per cent (18%) of patients developed febrile neutropenia in the first course of chemotherapy and 66.7% of these patients then experienced febrile neutropenia during the second course of chemotherapy. Alternatively, of the 82% of patients who did not experience febrile neutropenia during the first course of chemotherapy, only 7.1% subsequently developed such a complication. The predictive performance

of such a model can be judged in terms of a measure termed the likelihood ratio. For predicting a positive outcome, the likelihood ratio is simply the model sensitivity divided by one minus the model specificity. Simple calculations show that the risk threshold for febrile neutropenia falls as the likelihood ratio increases above 1. The likelihood ratio of a previous episode of febrile neutropenia based on the experience reported above is found to be 9.39, corresponding to a risk threshold of 8.7%, based on the strategy of treating patients with filgrastim only after such an episode (Fig. 2). Therefore, the introduction of a clinical prediction model, based upon an episode of febrile neutropenia, can dramatically decrease the risk threshold and, therefore, improve the cost efficiency of filgrastim treatment.

There is limited prospectively validated information on predicting a patient's risk of chemotherapy-related complications. Blay and colleagues identified two independent risk factors for febrile neutropenia: day 5 lymphocyte count $\leqslant 700/\mu l$ and type of chemotherapy. The model was validated in a group of patients receiving a variety of chemotherapy regimens for different tumour types, including a minority of breast cancer patients and a group of lymphoma patients [18]. Further validation was obtained in patients treated at various cancer centres and general hospitals [19]. Patients with both risk factors were at high risk of febrile neutropenia ($>40\%$) and the question of whether these patients would benefit from primary prophylaxis with haematopoietic growth factors is being addressed in a prospective phase III trial. The same group has proposed a risk model for chemotherapy-induced thrombocytopenia, with four factors predictive of high risk for platelet transfusions: day 1 platelet count $<150\,000/\mu l$, day 1 lymphocyte count $\leqslant 700/\mu l$, type of chemotherapy and performance status >1 [20].

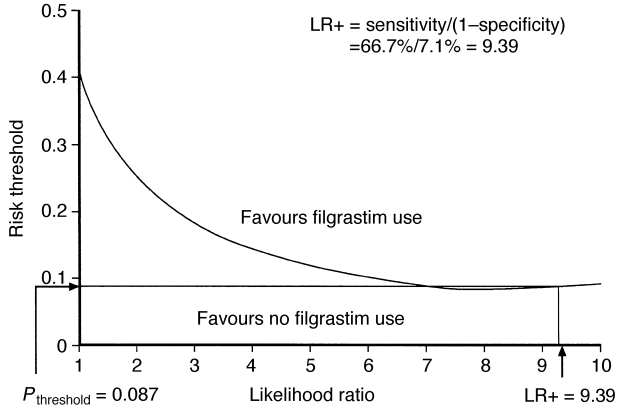

Fig. 2. Cost-minimisation analysis with filgrastim in secondary prophylaxis following an episode of febrile neutropenia. Two-way sensitivity analysis indicating the threshold curve for treatment with filgrastim only in those experiencing a previous episode of febrile neutropenia. The risk threshold decreases as the model performance (likelihood ratio) increases. (P-Test $=0.2$; hospital cost = US$ 1000/day.) Adapted from [17].

6. Predictive models in early breast cancer

Clinical prediction models can be readily extended to cost-effectiveness studies where treatment may impact on clinical effectiveness. A clinical prediction model developed and validated in women receiving adjuvant chemotherapy for breast cancer, and the potential cost-effectiveness of filgrastim used selectively to sustain dose intensity, were recently reported by Silber and colleagues in two companion papers [21,22]. In the first study, a conditional predictive model for subsequent neutropenic complications (absolute neutrophil count or ANC $\leqslant 250/\mu l$, dose reduction ($\geqslant 15\%$) or treatment delay ($\geqslant 7$ days) was developed in 95 women receiving adjuvant chemotherapy for breast cancer, utilising baseline clinical characteristics, as well as the results of the first cycle of therapy. 39 out of the initial 95 patients (41%) experienced at least one neutropenic complication during the first course of treatment. Fifty-six per cent ($n=22$) of these 39 patients subsequently experienced a second event. Variables found to be significant independent predictors of subsequent neutropenic complications included the concurrent administration of radiation therapy, the magnitude of decrease in haemoglobin level during the first cycle compared with baseline values and the nadir ANC during the first cycle (Table 1). The first-cycle ANC nadir was the most significant predictor for subsequent neutropenic complications (Fig. 3). Patients who received radiation therapy had a greater risk of experiencing subsequent neutropenic complications regardless of the ANC nadir during the first course. The authors concluded that it was possible to rank patients according to their risk of subsequent neutropenic complication and, therefore, their need for supportive care with filgrastim, based on blood counts observed in the first cycle of therapy.

Following validation of the predictive model in a similar population, the cost-effectiveness of filgrastim use was studied by Silber and colleagues [22]. The authors compared the cost of using filgrastim according to a specific strategy with a traditional dose-reduction alternative without filgrastim. A threshold risk of a

Table 1
Clinical prediction model[a] for neutropenic event (severe neutropenia with ANC $\leqslant 250/\mu l$, treatment delay $\geqslant 7$ days or dose reduction $\geqslant 15\%$) after cycle 1 [21]

	Relative risk	P value	(95% CI)
Radiation + chemotherapy	9.48	0.0011	(2.46–36.6)
First-cycle ANC	4.40	0.0001	(2.11–9.20)
Haemoglobin drop at nadir	1.80	0.0074	(1.17–2.77)

ANC, absolute neutrophil count; CI, confidence interval.

[a] Logit = 0.6407 + 2.2496 (radiotherapy + chemotherapy) −1.6309 (ANCNAD1) −0.9903 (HDROP1) where ANCNAD1 is the first-cycle ANC nadir and HDROP1 is the fall in haemoglobin during cycle 1.

neutropenic event was calculated for each patient based on the results of the predictive model. When allowed, filgrastim would be added to treatment if the risk of a neutropenic complication was above a threshold risk or if an event actually occurred.

Baseline filgrastim assumptions considered in the model included: (1) filgrastim would not be used during the first course of treatment; (2) filgrastim would be given to the highest risk 50% of patients; and (3) the use of filgrastim would reduce the probability of a neutropenic complication by 50%. Other assumptions incorporated into the model included those related to dose reduction, survival and cost. Under the no-filgrastim strategy, patients who experience a neutropenic event would have a 25% dose reduction followed by a 50% reduction with a second event. Under the filgrastim strategy, those considered to be at low risk after the first course of therapy would not receive filgrastim unless a neutropenic event occurred, after which the dose of chemotherapy would be reduced by 10%. A second neutropenic event would subsequently lead to a 50% reduction in dose. Alternatively, those considered at high risk would receive filgrastim immediately after the first course of therapy. The first neutropenic event in these patients would lead to a 25% dose reduction and the second event to a 50% reduction in chemotherapy dose. It was assumed that a 50% reduction in the relative dose intensity would result in a decrement in 3-year disease-free survival from 75 to 64% or an 11% decrease. This assumption was based on a study conducted by the Cancer and Leukemia Group B (CALGB), where women were randomised to adjunctive cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) at relative dose intensities of 100%, 67% and 50% [23,24]. The Silber study also assumed that recurring patients would survive at least 3 years followed by an exponential mortality rate and that patients not dying of breast cancer would die of other causes dictated by life expectancy data. The costs of drugs and associated treatment were based on Red Book prices and Medicare DRG reimbursement.

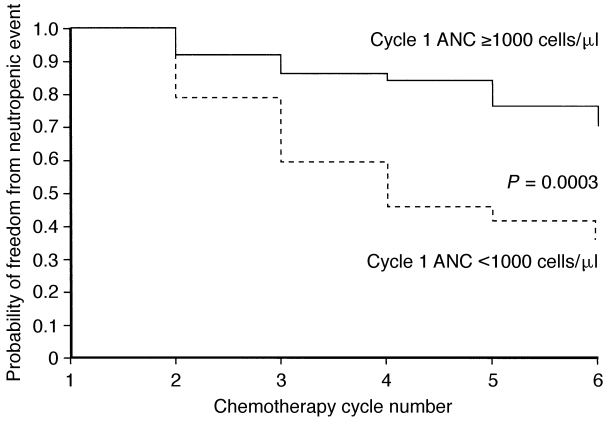

Fig. 3. Predictors for neutropenic complications in patients with early-stage breast cancer. The fall in absolute neutrophil count (ANC) during the first course of chemotherapy is the best predictor for the risk of subsequent neutropenic events [21].

When the filgrastim use strategy was applied on the basis of treating the neediest 50% of patients with filgrastim, a cost-effectiveness ratio of US$ 34 297 per life year saved (Euro 32 002) is estimated. As shown in Fig. 4, the cost-effectiveness ratio increases as the proportion of patients receiving filgrastim increases. Likewise, the cost-effectiveness ratio increases with increasing age and weakening assumptions about the impact of dose reduction on disease-free survival. The authors concluded that the model results are relatively insensitive to hospital cost estimates. However, the model is limited by the assumptions about the shape of the relationship between chemotherapy dose and survival. Further prospective data about the shape of the dose–response curve in women receiving adjuvant chemotherapy for breast cancer is needed. It will also be important to evaluate this predictive model in prospective clinical trials.

Nevertheless this study indicates that the administration of filgrastim to women receiving breast cancer adjuvant chemotherapy who are at greatest risk for neutropenic complications based on a valid clinical prediction measure is potentially cost-effective. The cost-effectiveness ratio of US$34 297 per life year saved (Euro 32 002) is well within the generally accepted range of cost-effectiveness for the treatment of cancer (Fig. 5) and other common medical conditions. For example, the cost-effectiveness of kidney dialysis for patients with end-stage renal disease is reported to be US$45 000 per life year saved (Euro 41 989) [25].

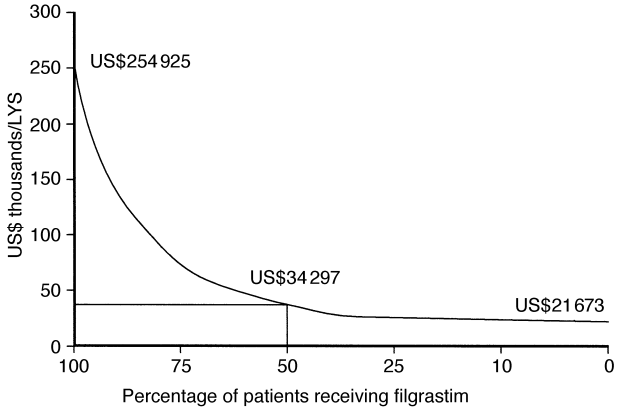

Fig. 4. Cost-effective use of filgrastim in patients with early-stage breast cancer: the association between the percentage of patients receiving filgrastim and the mean incremental cost per life year saved (LYS). If all patients were treated with filgrastim starting at course 2, the average cost-effectiveness ratio would be US$254 925/LYS (Euro 237 869). If all patients must first develop an event before filgrastim use, then the mean increment would be US$21 673/LYS (Euro 20 222). If the 50% of patients at greatest risk are given filgrastim, the mean increment would be US$34 297/LYS (Euro 32 002). These calculations are based on an age at diagnosis of 55 years [22].

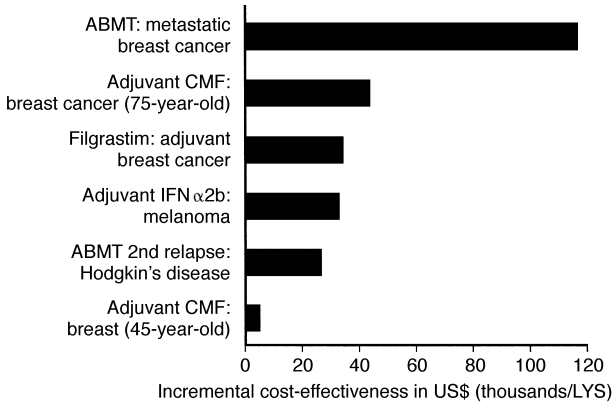

Fig. 5. Cost-effectiveness of common medical interventions for cancer treatment. The estimated cost-effectiveness of filgrastim in women receiving adjuvant chemotherapy for breast cancer based on a clinical prediction model is compared with that of several forms of cancer treatment. ABMT, autologous bone marrow transplantation; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; IFN, interferon.

7. Summary and conclusions

It is increasingly evident that methods of economic analysis can be used to evaluate management strategies in cancer therapy. Physicians are unlikely to use expensive treatments unless there is some justification in terms of cost-effectiveness. Moreover, in the absence of economic evidence, health authorities, insurance companies and professional groups may advise against the use of these agents owing to excessive costs. Previous cost-minimisation studies have indicated that filgrastim use actually reduces cost in specific clinical situations. The risk thresholds for cost savings with filgrastim can be shown to decrease by nearly one-half of the original value of 40% when hospital costs are high or when patients require lengthy hospitalisation for febrile neutropenia. Clinical prediction models represent a tool for improving patient selection for filgrastim treatment which can further decrease febrile neutropenia risk thresholds. Clinical prediction models have recently been extended to a study of the cost-effectiveness of selective filgrastim use in women receiving adjuvant breast cancer chemotherapy. The strategy of selecting women for filgrastim who are at high risk for neutropenic complications using a valid clinical prediction model based on first-cycle blood counts was shown to be potentially cost-effective compared with other healthcare technologies. Such a strategy may also improve clinical outcomes by permitting the safe administration of full-dose chemotherapy on schedule. Further research is needed to define more fully the role of filgrastim in breast cancer therapy and to extend the model to other tumour types. However, physicians need to look beyond mere cost-minimisation to evaluate the impact of a regimen on patient survival and quality of life [26]. Current clinical practice guidelines should be re-evaluated in the light of recent findings. The use of filgrastim should be considered in any patient receiving systemic chemotherapy for a potentially curable malignancy when it is considered necessary to sustain dose intensity.

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