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The Impact of Therapy with Filgrastim (Recombinant Granulocyte Colony-stimulating Factor) on the Health Care Costs Associated with Cancer Chemotherapy

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The objective of the study was to estimate the net impact on health resource utilisation of using recombinant granulocyte colony-stimulating factor (filgrastim) following myelosuppressive chemotherapy. Cost minimisation of the study medication in a randomised, double-blind, placebo-controlled clinical trial was conducted in teaching institutions and affiliated community hospitals participating in a clinical trial. 68 patients with small cell lung cancer undergoing cyclophosphamide, doxorubicin and etoposide chemotherapy were randomised to blinded placebo or filgrastim study medication at three or 14 clinical trials sites. The patients received daily subcutaneous injections of filgrastim or placebo, initiated 24 h after chemotherapy and continued until the neutrophil count exceeded 10000 × 10^6/l after the time of the expected nadir. Differences in total charges, costs and Medicare payments between treatment groups were the main outcomes measured. Compared to placebo patients, filgrastim-treated patients had significantly fewer and less resource-intensive hospitalisations. After accounting for filgrastim purchase and administration, the charge model predicts overall savings from filgrastim use in a clinical setting in which the risk of febrile neutropenia is high for patients not receiving filgrastim. The Medicare and cost models predict only a partial recapture of the cost of filgrastim therapy. The health care resources impact of filgrastim was sensitive to the risk of hospitalisation with febrile neutropenia, and to the perspective chosen for measuring resource utilisation (charges, costs or Medicare payments). The adjunctive use of filgrastim following myelosuppressive chemotherapy leads to partial or complete recapture of the cost of purchasing and administering the product.
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INTRODUCTION

THE COSTS of cancer diagnosis and treatment in the U.S.A. are rising, with total expenditures estimated at $35 billion in 1990, an increase of 62% compared to 1985 [1]. Several factors contribute to these high cancer-related costs, including the severity and progressive nature of the underlying disease with its frequent co-morbidities, the intensive utilisation of professional services, multiple diagnostic testing, the purchase and administration of traditional chemotherapeutic agents and newer biological therapies, and the complications of these cancer treatments. Myelosuppression, with consequent hospitalisation for infections manifested by febrile neutropenia, is one frequent, potentially life-threatening and particularly costly complication of cancer chemotherapy. Hence, any therapy that decreases the incidence, severity or duration of myelosuppression has the potential both to improve the care of the oncology patient and to recover some of the costs of that therapy.

Haematopoietic growth factors are glycoproteins that regulate the production and function of blood cells [2, 3]. Several of these proteins have been cloned and studied in clinical trials. In phase II studies, both recombinant granulocyte–macrophage colony-stimulating factor and recombinant granulocyte colony-stimulating factor (filgrastim) have been shown to decrease the duration and severity of neutropenia following cancer chemotherapy [4–6]. In a multicentre, randomised, double-blind, placebo-controlled clinical trial, the use of filgrastim following chemotherapy in patients with small cell lung carcinoma was found to be associated with a reduction in the incidence of febrile neutropenia and culture-confirmed infection, and in the total number of days of treatment with intravenous antibiotics and days of hospitalisation [7]. These findings of clinical benefit, associated with filgrastim use, suggest that this therapy may also decrease utilisation of some health care resources.

The purpose of this study is to assess the resource savings associated with filgrastim use, and to estimate the degree to which these savings recapture the costs associated with the acquisition and use of filgrastim. The magnitude of this overall cost impact was measured using hospitalisation data from patients with febrile neutropenia at three of the study sites involved in the randomised, double-blind, placebo-controlled clinical trial. The cost analysis was conducted from the perspective of a payer responsible for the costs associated with filgrastim therapy, and the costs of the treatment of febrile neutropenia. The

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implications of the results of the analysis for the heterogeneous setting of clinical oncology were explored through a univariate sensitivity analysis.

MATERIALS AND METHODS

The study assumed the perspective of the payer for health care services. We analysed hospital and physician charges incurred during the phase III clinical trial, and then estimated the cost of filgrastim therapy. The cost impact was estimated from the perspective of the third party payer, with the assumption that the payer would incur the costs of filgrastim therapy, and of the any treatment required for febrile neutropenia. We constructed a decision analysis model to estimate the cost impact of the decision to utilise filgrastim, following a cycle of chemotherapy, from this perspective. We then utilised a sensitivity analysis to examine the implications of our findings, altering one variable at a time.

Clinical trial overview

The cost analysis was conducted in conjunction with a phase III clinical trial examining the safety and efficacy of filgrastim. Details of this trial and its findings have been published elsewhere [7]. In that study, patients with small cell lung cancer were stratified, based upon performance status and the presence or absence of bone marrow involvement with the tumour, and then randomised to receive either placebo or filgrastim during each cycle of chemotherapy. The chemotherapy regimen comprised of cyclophosphamide 1000 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, and etoposide 120 mg/m^2 on days 1, 2 and 3 of each chemotherapy cycle. The cycles were repeated every 21 days for up to six cycles, provided that sufficient haematological recovery had taken place following the previous cycle, and that tumour progression had not occurred. On day 4 of each chemotherapy cycle, patients began daily subcutaneous injections of the blinded study medication, filgrastim or placebo. Injections continued until the absolute neutrophil count rose to more than 10 000 $\times$ 10^6/l, after the time of the expected neutrophil nadir.

Patients were monitored closely. Complete blood counts were obtained three times weekly. Patients kept daily written records of their body temperatures. Any patient reporting a temperature elevation to 38.2°C or greater was examined immediately by a physician, and a blood count was obtained. If the absolute neutrophil count associated with this fever was less than 1000 $\times$ 10^6/l, the patient was hospitalised and treated with standard intravenous antibiotics while continuing the daily injection of the blinded study medication. For patients experiencing febrile neutropenia, the randomisation code was broken at the beginning of the next chemotherapy cycle, and the patient was removed from the blinded portion of the study. At the time of discharge from hospital, following an episode of febrile neutropenia, the randomisation code had not been broken.

Collection of hospital and physician bills

We obtained itemised hospital and physician bills for all hospitalisations of patients with febrile neutropenia which occurred at Duke University Medical Center, UCLA Medical Center, and University of Pittsburgh (with enrollments of 24, 25 and 19 patients, respectively) or at associated community hospitals. We eliminated charges for radiological procedures that were conducted as part of the clinical trial protocol, and not as part of the standard care for patients during hospitalisation for febrile neutropenia, as well as any charges associated with inpatient chemotherapy. The review of invoices was carried out by one of the authors who was blind as to the study medication the patient had received.

Hospital and physician bills were collected during all chemotherapy cycles. Because of the design of the clinical trial, some patients were removed from each group in the double blind study with each cycle of chemotherapy. Hence, our cost analysis focused on the first chemotherapy cycle, as this was the cycle during which the placebo and filgrastim groups were balanced with respect to initial stratification criteria, and most representative of the general population of patients treated with chemotherapy. The crossover design of the clinical trial precluded us from measuring charges in an unbiased placebo group in any cycle other than the first.

Determining the price of filgrastim therapy

Because filgrastim was provided free of charge during the trial, it was necessary to estimate the charges that would have been incurred had the product been available commercially and charged to the third party payer. In the clinical trial, the mean duration of filgrastim therapy in patients randomised to receive that medication was 11.7 days [7]. The dose received by these patients was approximately the dose of filgrastim now recommended on the package insert, 5 μg/kg/day [8]. As currently supplied, filgrastim is available in two single dose vial sizes, one containing 300 μg with an average wholesale price (AWP), at the time the hospital charge data was being collected, of $130, and the other containing 480 μg, with an AWP of $206 [9]. Hence, if the filgrastim were used as recommended on the package insert, and as used in the clinical trial, patients weighing 60 kg or less would require purchase of a 300 μg vial for each day of filgrastim therapy, and heavier patients would purchase a 480 μg vial each day. In the clinical trial, 21% of the patients weighed 60 kg or less, and 79% weighed more than 60 kg. The cost of filgrastim acquisition was calculated based upon these data, utilising an average daily expenditure for filgrastim reflective of this measured patient weight mix (Table 1).

In addition to the cost of acquiring filgrastim itself, there were other costs associated with the use of that medication, and which were included in the cost analysis. The package insert recommends that patients be monitored with additional complete blood count (CBC) determinations, and patients require injection supplies (insulin syringes and alcohol wipes). In addition, patients may require additional education in self injection and additional physician time may be necessary for this purpose. After consulting Medicare fee schedules, we determined that $20 is a typical charge for each CBC; it was estimated that three additional CBCs would be required per chemotherapy cycle, and $60 was added to the cost of filgrastim therapy in the determination utilising charges. A telephone survey of community pharmacies determined that $3.50 would be required for purchase of sufficient insulin syringes and alcohol wipes for one cycle of filgrastim. The average submitted charge for an intermediate office visit listed in the 1987 Part B Medicare Annual Data (BMAD) file is $22, and this charge was used to represent the charges associated with patient education. In the clinical trial, filgrastim therapy was not associated with any toxicities requiring health care resource use, and no cost for treatment of filgrastim was considered in the cost analysis.

Statistical methods

Statistical comparisons were made using the non-parametric Mann–Whitney U test in Statview II statistical software (Abacus

Table 1. Charges and length of stay for cycle 1 hospitalisation with febrile neutropenia for patients followed at three study sites in a randomised, double-blinded, clinical trial

	Patients receiving filgrastim (n=36)	Placebo patients (n=32)	Difference between placebo and filgrastim	P values*
Analysis per hospitalisation with febrile neutropenia				
Number of hospitalisation	5	22		
Average hospital and physician charges	$4258	$8469	$4211	0.005
Average length of stay (days)	3.6	7.3	3.7	0.001
Analysis per enrolled patient				
Average hospital and physician charges	$591	$5822	$5231	0.0001
Average length of stay (days)	0.5	5.0	4.5	0.0001
Expenses of filgrastim therapy				
Product price, tests, supplies, patient education	$2302	$0	$2302	n.a.†
Average total charge per enrolled patient for filgrastim therapy and treatment of febrile neutropenia	$2893	$5822	$5292	0.0001‡

*Calculated using Wilcoxon rank sum test. †Not calculated because filgrastim charges were imputed and not observed; n.a., not available. ‡Estimated assuming filgrastim therapy expense of $2302 per patient.

Concepts, Berkeley, California, U.S.A.). The level of significance for all comparisons was set at 0.05.

Economic analysis model

Two types of sensitivity analysis were conducted, an economic analysis model and a univariate sensitivity analysis. The economic analysis model was developed to examine the generalisability of the hospital billing data collected during the clinical trial. This model, illustrated in Fig. 1, can be reduced to a single expected value for each treatment arm. By subtracting the estimated total resources used for filgrastim treatment from the estimated total resources for the placebo group, we obtained the net cost impact associated with filgrastim use during a cycle of myelosuppressive chemotherapy. In all analyses, the cost impact was calculated from the standpoint of the third party payer, and with the assumption that this payer would be responsible for paying for both the treatment of infectious complications of chemotherapy and for filgrastim therapy. The model examined total resource consumption and did not distinguish between payments made by the payer and deductibles and co-payments made by patients.

Three health care financing perspectives were analysed: a 'charge' model, a 'Medicare' model and a 'cost' model. These perspectives were chosen in recognition of the fact that patients and third party insurers pay for health care services using different payment mechanisms. In all three models, it was assumed that the rates of hospitalisation with febrile neutropenia were the ones measured in the first cycle of the double-blind randomised clinical trial [7]. During this cycle, filgrastim and placebo groups were balanced with respect to initial stratification criteria, and were most representative of the general population of cancer chemotherapy patients. The rates of febrile neutropenia during this cycle in the filgrastim group were 0.26 and 0.55 in the placebo group (P and P^*, respectively, in the economic model). The theory behind each approach is discussed below. Appendix 1 summarises the data and estimations used in the base model for each perspective.

Charge model. In the charge model, resource utilisation was estimated based upon the invoiced charges of hospitals and physicians, collected and analysed as described above. This model differs from the previously described analysis of charges incurred during the clinical trial only in that the rate of hospitalisation with febrile neutropenia employed is the rate observed in all patients enrolled in the double-blind clinical trial.

Medicare model. In the Medicare model, resource use was measured by the diagnosis-related group (DRG) payments made by the Medicare program. Hospital payments were assumed to equal the average payment for DRG 398 (reticuloendothelial immunity disorders with complications and comorbidities) at the institutions where each clinical trial patient was hospitalised [10]. Physician services were estimated based upon Medicare's national average allowable rates as listed in the 1987 BMAD file and the length of stay for each hospitalisation. It was assumed that physicians would perform an initial comprehensive visit ($104), and a follow-up visit on each subsequent hospital day ($30).

Cost model. In the cost model, resource use was estimated as the true 'costs' incurred by study hospitals and physicians in providing the goods and services used by the study patients. Hospital costs were obtained by multiplying each hospital's charges by its overall cost-to-charge ratio listed in Medicare cost

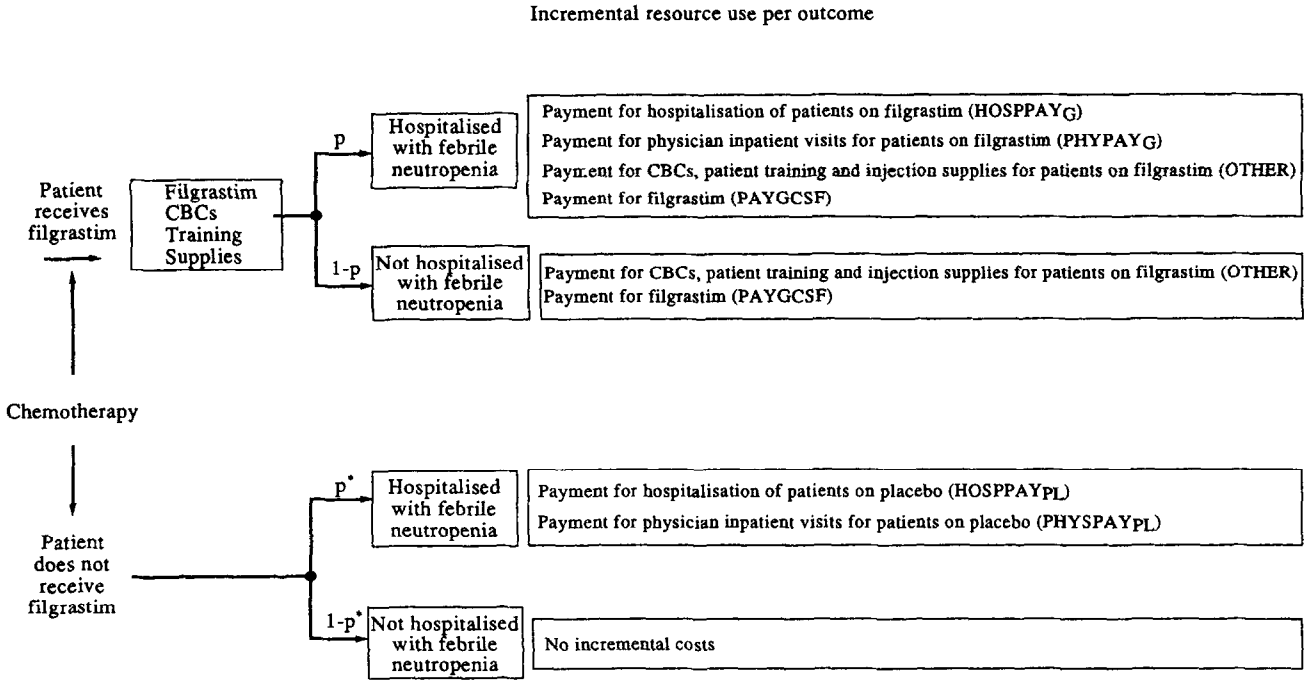

Fig. 1. The decision analysis model for predicting incremental resource utilisation associated with filgrastim therapy following myelosuppressive chemotherapy.

potential values. The six variables included: (1) patient weight; (2) duration of filgrastim therapy; (3) price paid per vial of filgrastim; (4) rate of hospitalisation with febrile neutropenia among patients not treated with filgrastim; (5) percentage reduction in the hospitalisation rate associated with filgrastim use; and (6) the relative charge for hospitalisation with febrile neutropenia among patients treated with filgrastim compared to patients not treated with this product.

Comparison of charges to other reports

To evaluate the representativeness of the charge data collected at study hospitals, we examined claims for Medicare patients hospitalised nationwide under DRG 398, utilising the 1989 Medicare Provider Analysis and Review (MEDPAR) file.

RESULTS

Analysis of charges during the clinical trial

Charge data were collected for 68 patients at the three study sites and the data are summarised in Table 1. In this group of patients, the hospitalisation rate in the first cycle of chemotherapy among patients receiving filgrastim was 14% (5/36), compared to a rate in patients receiving placebo of 69% (22/32, $P = 0.0001$). In addition, those hospitalisations that did occur were, on average, approximately half as long and expensive as placebo patients' hospitalisations (means 3.6 versus 7.3 days, $P = 0.005$; \$4258 versus \$8469, $P = 0.001$).

Because of this reduction in both the risk and length of hospitalisation, the average number of hospitalisation days and average total charges among cost study patients receiving filgrastim were approximately one-tenth as great as the days and charges of cost study patients receiving placebo ($P < 0.0001$). After accounting for the purchase of filgrastim and associated tests, supplies and patient education, the average patient receiving filgrastim represented a net outlay per chemotherapy cycle for filgrastim and care of febrile neutropenia of \$2893 compared with \$5822 for patients on placebo. The difference in net outlays of \$2929 per cycle is the predicted charge savings associated with filgrastim therapy in these 68 patients.

Impact of filgrastim as measured in the economic analysis model

The results of the three sets of economic analysis models are presented in Fig. 2. Economic impacts above \$0 reflect savings over and above the full recapture of the cost of filgrastim, those at \$0 are revenue neutral (i.e. full cost recapture), and those below \$0, up to \$2302 (the predicted per cycle cost of filgrastim therapy), represent a partial recapture of the cost of filgrastim therapy. Uniformly, the economic savings per cycle associated with filgrastim as seen in the three models are substantially lower than the savings seen in the analysis of charges collected during the trial (Table 1). The Medicare model suggests that filgrastim therapy results in incremental costs of \$602 per patient per cycle.

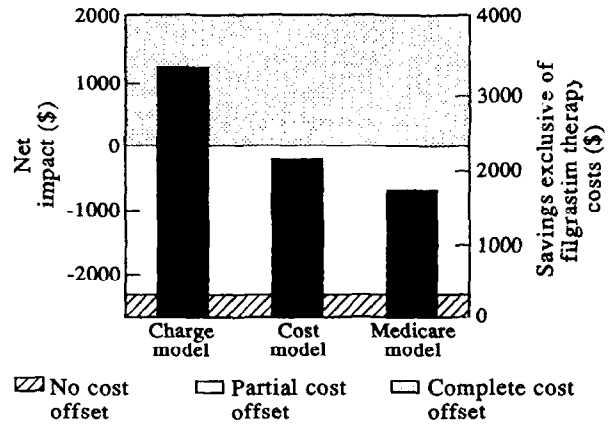

Fig. 2. Impact of filgrastim on first cycle savings in the charge, cost and Medicare economic analysis models.

In these patients, filgrastim therapy reduces the number of hospitalisations but, because of the fixed DRG payment mechanism employed, does not reduce the cost to Medicare for the hospitalisations that do occur. In the cost model, filgrastim therapy results in an additional cost of $138 per cycle of chemotherapy. The charge model, which utilises hospitalisation risk data from the larger clinical trial [7] rather than the measured rates in our subgroup of 68 patients, yields a net savings of $1250 per chemotherapy cycle.

Univariate sensitivity analysis

Figure 3 provides results of six univariate sensitivity analyses. In the six analyses, the estimated impact ranges from partial to more than total recapture of the cost of filgrastim therapy. As was the case in the baseline economic analysis model, the net recapture of filgrastim expenditures in the cost analyses were lower than in the charge analyses but greater than in the Medicare analyses.

Three analyses of factors important in filgrastim therapy, dose (determined by patient weight), duration of treatment and product price, are shown if Fig. 3a–c. The filgrastim is currently supplied in single dose vials in two sizes; therefore, the effect of patient weight on savings is a step function, with increases in filgrastim cost, and consequent decreases in the magnitude of cost recapture, associated with weight above 60 kg (300 mg vial) and 96 kg (480 mg vial). The duration of filgrastim therapy is determined by the rate of recovery of neutrophil counts following chemotherapy. While in the charge model filgrastim therapy is associated with full recapture of costs throughout the range of durations explored, in the Medicare and cost models, filgrastim therapy is associated with full recapture only when the duration required is less than 9 and 11 days, respectively (Fig. 3b). Similarly, through the plausible range of payment levels for filgrastim, full cost recapture is predicted by the charge model, but additional resource use (partial recapture) is predicted in the cost and Medicare models (Fig. 3c).

Three analyses examine the impact of factors reflecting the efficacy of filgrastim therapy, including the risk of hospitalisation with febrile neutropenia if filgrastim is not employed (Fig. 3d), the effect of filgrastim on the risk of hospitalisation (Fig. 3e) and the effect of filgrastim on resource utilisation during hospitalisation (Fig. 3f). In the clinical trial, filgrastim reduced the risk of hospitalisation by approximately 50%. Assuming this effect of filgrastim on hospitalisation risk, this therapy more than recaptures its cost only when the risk of hospitalisation in placebo patients exceeds 35% in the charge model, 60% in the cost model, and 70% in the Medicare model. In the clinical trial, 55% of patients receiving placebo were hospitalised with febrile neutropenia during the first chemotherapy cycle. Assuming this 55% risk of hospitalisation without filgrastim, filgrastim more than recaptures its cost in the charge model, even when it decreases the hospitalisation rate by 25%. To generate total cost recapture in the other models the differences in hospitalisation rates with and without filgrastim must be greater. Figure 3f shows that savings in the charge and cost models vary with the relative costliness of filgrastim hospitalisations as compared with placebo. However, because Medicare provides the same DRG payment regardless of resources consumed, the Medicare curve is flat.

DISCUSSION

Two randomised clinical trials have shown that filgrastim provides significant benefit by reducing the infectious complications of chemotherapy as manifested by febrile neutropenia, and that this leads to an associated reduction in days of hospitalisation and antibiotic treatment [7, 12]. An analysis was undertaken to determine the net impact on treatment costs when filgrastim is used as an adjunct to cancer chemotherapy. Our major finding is that, from the perspective of a payer responsible for the cost of the filgrastim and of hospitalisations for febrile neutropenia, the clinical benefits of filgrastim can lead to the recapture of at least 70% of this product's cost and, in some settings, it may actually produce overall cost savings. The analyses show that when filgrastim is used as an adjunct to cancer chemotherapy, there are important savings in health care resources which must be considered and the magnitude of these savings relative to the cost of filgrastim therapy depends on clinical variables, as well as on the method for modelling the cost of hospitalisation. We chose three models for calculating the cost of febrile neutropenia to the payer, utilising charge data, 'cost data' (derived from charge data), and Medicare data.

There is tremendous heterogeneity in health care reimbursement plans; the charge and cost models were constructed to flank the upper and lower limits of these plans, including managed care reimbursements, and to provide a feasible range of predicted cost impacts. In our study, in the analysis based upon charges, there is both improved clinical outcome and full recapture of the costs of filgrastim therapy; the product is both cost-effective and cost saving. Using alternative analyses based on the 'cost' of a hospitalisation, the savings associated with reduced hospitalisations lead to only a partial recapture of the expense of administering filgrastim, resulting in a net increase in total costs. In this case, filgrastim may still be viewed as cost-effective if the clinical benefits are deemed worth the additional expense.

In this study, an analysis of billed charges at three sites suggests that filgrastim leads to savings of $2929 per patient in the first chemotherapy cycle. However, placebo patients at these three study sites experienced average hospitalisation rates that were higher, and filgrastim patients rates that were lower, than those observed in the overall clinical trial. Together, these differences in hospitalisation rates led to a large and statistically significant difference in charges between the two groups. In contrast, in the economic analysis model, the rates of hospitalisation for the two groups observed in the entire clinical trial were applied, and the predicted cost savings per chemotherapy cycle associated with filgrastim were calculated based upon this larger clinical experience. We believe the economic analysis model results are more reliable, as the sample size used to generate the risk of hospitalisation is larger.

Our data were generated during a clinical trial of a particular chemotherapy regimen given to patients with small cell carcinoma of the lung. In generalising our results to other chemotherapy regimens and tumour types, it is important to note that some aspects of our methodology may lead to an overestimation of the degree to which the cost of filgrastim is recaptured in other resource savings. The most important of these is the chemotherapy regimen employed, and the relatively high observed rate of hospitalisation with febrile neutropenia in the placebo group. The chemotherapy doses were chosen to represent an aggressive standard for cyclophosphamide-based chemotherapy in small cell lung cancer; a recent literature review suggests that this goal was met, as similar doses can be found in other studies [13]. Although the 55% rate of hospitalisation with febrile neutropenia is high, the literature suggests that it is representative of some chemotherapy regimens, and some report

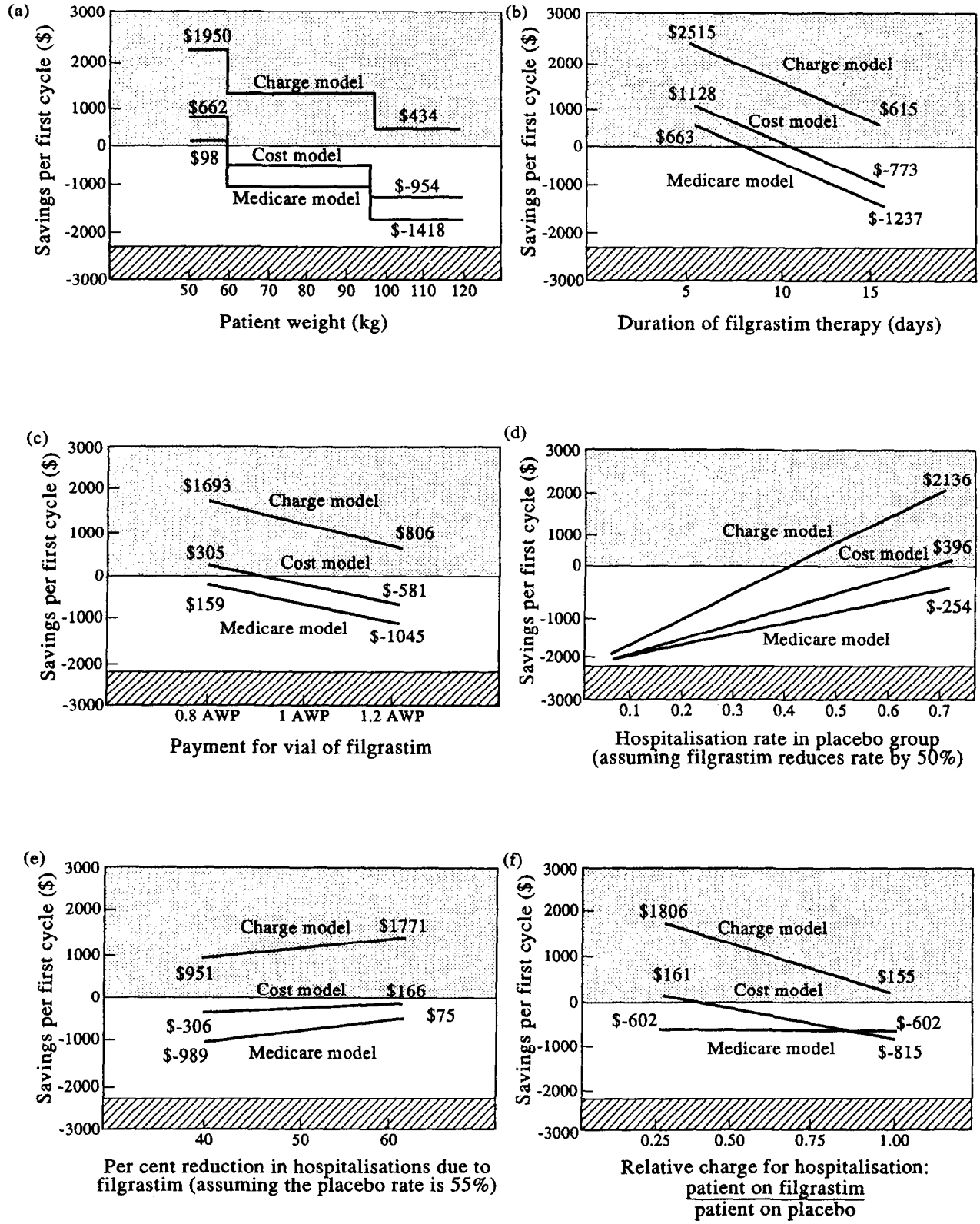

Fig. 3. Sensitivity analyses demonstrating filgrastim impact under charge, cost and Medicare models. In each panel a single variable is varied through a range of plausible values, with other variables held constant at baseline values. AWP, average wholesale price.

rates of neutropenia as high as 100% [14]. Rates of febrile neutropenia as high as 47% are reported, although most studies report rates to be 20% or less [14, 15]. It is likely that the high incidence of febrile neutropenia observed in the phase III study of filgrastim was due in part to the vigilance with which patients' temperatures and blood counts were monitored. Clinicians may have identified events that usually go unnoticed in community practice and less rigorous clinical trials. Regardless of the reasons for the high rate of febrile neutropenia in the placebo group, we recognise that the estimated impact of filgrastim on resource

utilisation may be greater than would be observed in other clinical settings, in which the risk of infection without filgrastim is lower. If the hospitalisation rate in the placebo group is below 37%, filgrastim is associated with a net increase in resources utilised, even in the charge model. For example, if a chemotherapy regimen is associated with a 20% rate of hospitalisation with febrile neutropenia, then the charge model predicts that filgrastim will increase charges by $1034. If the hospitalisation rate is 10%, then the use of filgrastim increases charges by $1668.

Two additional elements that could have led to an overestimation of the magnitude of cost recapture are that we collected charge data during a clinical trial and that the trial was conducted at hospitals with large teaching programs, both factors believed to result in higher than average charges. Nevertheless, data from the Medicare database suggest that the charges and lengths of stay observed in placebo patients at the three study sites are of the same order of magnitude as charges incurred by similar patients nationwide. The situation is different, however, with respect to DRG payments. In analyses not shown, we found that DRG payments at study hospitals are generally higher than average DRG payments across the country. This difference reflects the slightly higher DRG payments typically provided to teaching hospitals, and suggests that the predicted magnitude of r-metG-CSF cost recapture in the Medicare model may be somewhat overestimated.

There are additional factors which may have led to an underestimation of the extent to which filgrastim therapy recaptures its cost. In the Medicare analysis, we assumed that cases would be assigned to DRG 398, although some hospitals may code inpatient stays in ways that lead to assignment to higher paying DRGs. This is particularly true in elderly cancer patients, who frequently have other active medical problems that could justify higher reimbursement. Of course, a portion of that reimbursement would be needed to pay for other active medical problems. In all the models, we underestimated the professional fees of non-oncologists, an error that, if corrected, would increase the predicted filgrastim cost recapture. Further, we assumed that payment for the filgrastim would be based on the AWP. However, payments substantially lower than AWP occur with other medications, a situation that, if duplicated for filgrastim, would increase the magnitude of predicted cost recapture in all our models. For Medicare, which may reimburse only 80% of AWP, the modelled price of filgrastim was an overestimate; the full AWP was utilised in this model because it was assumed that a second payer, the patient or a secondary carrier, would be responsible for the remaining portion of the acquisition price. Finally, because our impact analysis was conducted from the limited perspective of the third party payer, we did not include the favorable impact of the decreased incidence of serious infection and hospitalisation on indirect cost factors, such as ability to work, or function in the home setting. These components of quality of life are important factors in a complete cost-effectiveness evaluation.

One clear limitation to the current study is its focus on the first chemotherapy cycle. However, results from the 14-site clinical study suggest that filgrastim continues to have a favorable impact on neutrophil recovery in later cycles, and that the same may be true for resource utilisation. Unfortunately, the cross-over design of the clinical trial precluded us from measuring charges in an unbiased placebo group in any cycle other than the first.

It is important to stress that this study of resource utilisation was done with filgrastim, used to decrease the morbidity of standard dose chemotherapy. The decision analysed in the economic model was the decision to use filgrastim following the administration of an already decided upon, constant dose of chemotherapy, not the decision to increase the administered dose of chemotherapy utilising filgrastim to keep toxicity constant. The charge data and economic models afford only limited insight into the cost impacts of filgrastim utilised to increase chemotherapy dose. If the results of carefully controlled clinical trials suggest that chemotherapy dose escalation faciliated by filgrastim leads to improved tumour response rate and increased patient survival, a resource utilisation analysis of that application of filgrastim should incorporate the increased costs of the additional chemotherapy, any increase in toxicity associated with its administration, and any savings associated with the improved patient outcomes. In addition, future studies may also test the cost impact of alternative therapeutic strategies, such as prophylactic oral antibiotics.

We conclude that the adjunctive use of filgrastim, administered after myelosuppressive chemotherapy but prior to the onset of neutropenia, results in decreased resource utilisation which leads to the partial recapture of the cost of filgrastim therapy. This decreased resource utilisation is due to fewer hospitalisations with febrile neutropenia and, for those hospitalisations that do occur, shorter lengths of stay. In analyses utilising either charges, cost estimates derived from charges, or Medicare reimbursements to estimate the economic impact of febrile neutropenia, filgrastim therapy led to either a partial or complete recapture of the costs associated with purchasing and administering this agent. For an individual patient receiving chemotherapy, the net economic impact of filgrastim use depends most importantly on how one measures resource consumption (charges, costs or Medicare payments) and on the probability of being hospitalised with febrile neutropenia if filgrastim is not used. Additional factors that affect resource utilisation include the dose of filgrastim (the patient's weight), the purchase price of the filgrastim, the duration of filgrastim therapy required for full haematopoietic recovery in that patient, and the resources utilised during hospitalisation with febrile neutropenia.

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APPENDIX

Summary of estimates used in the decision analysis model

	Charge model		Medicare model		Cost model	
	Filgrastim	Placebo (PL)	Filgrastim	Placebo (PL)	Filgrastim	Placebo (PL)
Hospitalisations						
Rate	$P = 0.26$	$P^* = 0.55$	$P = 0.26$	$P^* = 0.55$	$P = 0.26$	$P^* = 0.55$
Hospital payments (HOSPPAY)	\$3896	\$7859	\$5373	\$5373	\$2218	\$4712
Physician payments (PHYSPAY)	\$389	\$610	\$155	\$266	\$182	\$292
Payment for r-metG-CSF (PAYGCSF)	\$2216	—	\$2216	—	\$2216	—
Outpatient items/services (OTHER)						
Three complete blood counts	\$60	—	\$30	—	\$30	—
Patient training	\$22	—	\$17	—	\$17	—
Injection supplies	\$3.5	—	\$3.5	—	\$3.5	—

Cost savings of r-metG-CSF compared to placebo
$$= \{(p^* - p) \times (HOSPPAY_{PL} + PHYSPAY_{PL})\} + \{p \times (HOSPPAY_{PL} - HOSPPAY_{G})\} + \{p \times (PHYSPAY_{PL} - PHYSPAY_{G})\} - OTHER - PAYGCSF$$

Cost savings in charge model
$$= \{(0.55 - 0.26) \times (\$7859 + \$610)\} + \{0.26 \times (\$7859 - \$3869)\} + \{0.26 \times (\$610 - \$389)\} - \$85.5 - \$2216 = \$1250$$

Cost savings in Medicare model
$$= \{(0.55 - 0.26) \times (\$5373 + \$266)\} + \{0.26 \times (\$5373 - \$5373)\} + \{0.26 \times (\$266 - \$155)\} - \$50.5 - \$2216 = -\$602$$

Cost savings in cost model
$$= \{(0.55 - 0.26) \times (\$4712 + \$292)\} + \{0.26 \times (\$4712 - \$2218)\} + \{0.26 \times (\$292 - \$182)\} - \$50.5 - \$2216 = -\$138$$