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Cost-Effectiveness of Primary versus Secondary Prophylaxis with Pegfilgrastim in Women with Early-Stage Breast Cancer Receiving Chemotherapy

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ABSTRACT

Objective: Prophylaxis with granulocyte colony-stimulating factor (G-CSF) reduces the risk of febrile neutropenia (FN) in patients receiving myelosuppressive chemotherapy. We estimated the incremental cost-effectiveness of G-CSF pegfilgrastim primary (starting in cycle 1 and continuing in subsequent cycles of chemotherapy) versus secondary (only after an FN event) prophylaxis in women with early-stage breast cancer receiving myelosuppressive chemotherapy with a ≥20% FN risk.

Methods: A decision-analytic model was constructed from a health insurer's perspective with a lifetime study horizon. The model considers direct medical costs and outcomes related to reduced FN and potential survival benefits because of reduced FN-related mortality. Inputs for the model were obtained from the medical literature. Sensitivity analyses were conducted across plausible ranges in parameter values.

Results: The incremental cost-effectiveness ratio (ICER) of pegfilgrastim as primary versus secondary prophylaxis was $48,000/FN episode avoided. Adding survival benefit from avoiding FN mortality yielded an ICER of $110,000/life-year gained (LYG) or $116,000/quality-adjusted life-year (QALY) gained. The most influential factors included FN case-fatality, FN relative risk reduction from primary prophylaxis, and age at diagnosis.

Conclusions: Compared with secondary prophylaxis, the cost-effectiveness of pegfilgrastim as primary prophylaxis may be equivalent or superior to other commonly used supportive care interventions for women with breast cancer. Further assessment of the direct impact of G-CSF on short- and long-term survival is needed to substantiate these findings.

Keywords: breast cancer, cost-effectiveness, pegfilgrastim, primary prophylaxis.

Introduction

Severe neutropenia (low white blood cell count) is a major untoward effect of chemotherapy, predisposing patients to bacterial infections that can be life threatening. Severe neutropenia and febrile neutropenia (FN) (low white blood cell count and fever, indicators of potential infection) in particular often prompt physicians to reduce chemotherapy doses, which may lower tumor response rates in the metastatic setting and increase the risk of cancer relapse in the adjuvant setting. The granulocyte-colony stimulating factors (G-CSFs) can reduce the incidence, duration, and severity of chemotherapy-induced neutropenia and related complications [1–6].

In the recent American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and European Organization for Research and Treatment of Cancer (EORTC) guidelines, primary prophylaxis with G-CSF is recommended from the first cycle of chemotherapy when the overall risk of FN is at least 20% [1,7,8]. Although most clinical trials have evaluated G-CSF at the onset of chemotherapy (primary prophylaxis) compared with either no G-CSF or after an FN event, herein referred to as secondary prophylaxis, retrospective studies suggest that clinicians often use G-CSF later in the course of chemotherapy in response to severe neutropenia or after patients develop FN [1,7–10]. Using G-CSF as secondary prophylaxis will decrease G-CSF expenditures, but may also expose patients to more FN events, with associated morbidity and mortality risks and costs, and may also result in chemotherapy dose reductions or delays. Given these tradeoffs, the purpose of this study was to estimate the cost-effectiveness of pegfilgrastim (Neulasta, Amgen Inc., Thousand Oaks, CA) when used as primary versus secondary prophylaxis in women with early-stage breast cancer receiving myelosuppressive chemotherapy with a risk of FN of approximately 20% or higher.

Several studies have evaluated the economic impact of prophylactic G-CSF in the setting of myelosuppressive chemotherapy [11–23]. Nevertheless, these studies primarily compare the short-term costs of G-CSF versus potential near-term cost offsets associated with avoiding FN-related medical care. Other potential short- and long-term health effects associated with G-CSF include avoiding FN-related mortality and improving survival from delivering chemotherapy at the planned dose and schedule. We consider the cost-effectiveness of pegfilgrastim in the setting of primary prophylaxis for breast cancer patients receiving myelosuppressive chemotherapy.

Methods

Study Population

The study population included women aged 30 to 80 years with stage I to III breast cancer receiving myelosuppressive chemotherapy (e.g., docetaxel, doxorubicin/docetaxel, or docetaxel/doxorubicin/cyclophosphamide [TAC]) with an FN risk of approximately 20%. The reference patient was 49 years old with stage II breast cancer receiving six cycles of chemotherapy.

Design of the Decision Analysis Model

A decision analytic model was constructed from a health payer's perspective (Fig. 1). The model considered a woman with breast

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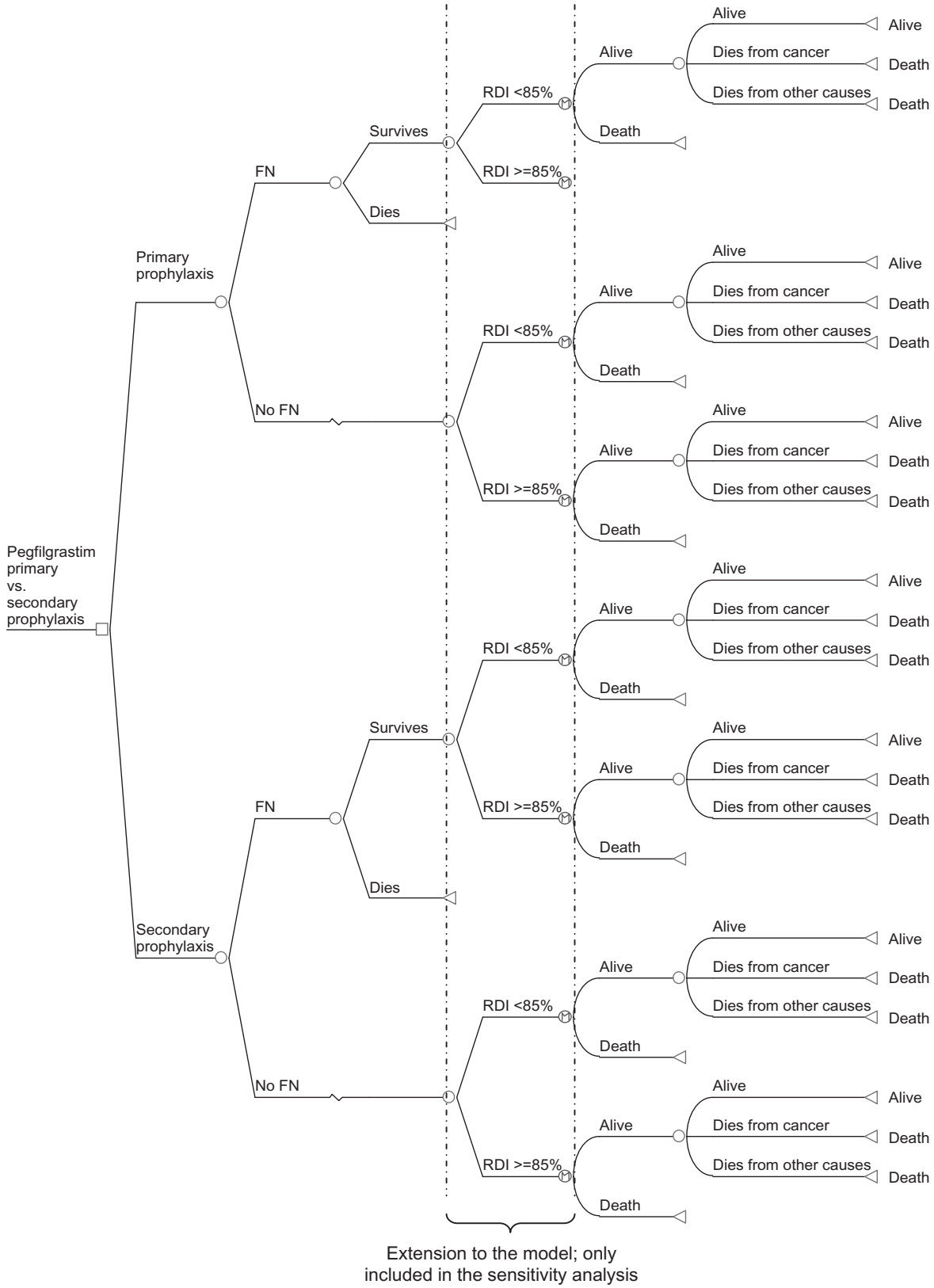

Figure 1 Model structure. FN, febrile neutropenia; RDI, relative dose intensity.

Table 1 Model inputs: health-care costs

Parameter	Point estimate	Range
Cost of pegfilgrastim per injection/cycle	$2142.24* [28]	(±30%) $1499.57, $2784.91
Cost of administration of pegfilgrastim/injection	$20† [29,30]	0, $100§
Hospital cost for an FN hospitalization (facility only)	$9745‡ [32]	$4000 [32,33], $20,000 [33]
Physician fees for an FN hospitalization (% of hospital cost)	10% [35]	0%, 15%§
Additional costs for subsequent FN-related care (as % of initial FN hospitalization cost)	40% [36]	0%, 40%
Cost of FN outpatient management (as % of initial FN hospitalization cost)	50% [36]	10% [37], 70%§

*2006 average sales price (ASP).
†CMS physician fee schedule, CPT 99211, CPT 90772.
‡Adjusted from 1999 value (i.e., $7100) to 2006 value using consumer price index (CPI) [27].
§Assumption.
CMS, Centers for Medicare and Medicaid Services; CPT, current procedure terminology; FN, febrile neutropenia.

cancer receiving myelosuppressive chemotherapy and considered two treatment strategies: pegfilgrastim primary prophylaxis and pegfilgrastim secondary prophylaxis. The model followed the patient until death from cancer or other causes. During the course of chemotherapy, the patient may experience an FN event, and as a result is at risk of dying from that event. As an extension to the model (used only in the sensitivity analysis), we also included the probability nodes for a patient to receive chemotherapy at a cumulative relative dose intensity (RDI) of <85%, which is defined as the amount (<85%) of chemotherapy delivered relative to the standard amount of chemotherapy over the course of chemotherapy.

The model was based on the FN incidence for a chemotherapy course (i.e., across all chemotherapy cycles). Patients who have one episode of FN are at risk for developing FN in subsequent cycles [24]. We indirectly modeled these recurring events by taking into account the cost associated with repeated hospitalizations. Nevertheless, the risk of mortality and chemotherapy dose reductions or dose delays associated with subsequent FN events was not captured by the model. Although most patients who develop FN are hospitalized, selected patients at lower risk of complications may be managed as outpatients [25,26]. We assumed that 80% of FN patients were hospitalized and 20% had outpatient management [15].

Health Care Costs

Costs included pegfilgrastim, drug administration, initial FN hospitalization, repeated FN hospitalizations, and subsequent FN-related medical costs, such as those at outpatient settings (Table 1). Direct nonmedical costs (e.g., cost of transportation) and indirect costs (e.g., lost productivity) were not considered. Although differences in chemotherapy doses would nominally affect the cost of chemotherapy, the need to waste whatever chemotherapy remained would likely limit this difference. In addition, the cost of adjunctive therapy and staff time would not be appreciably different even with the difference in chemotherapy dose. We therefore assumed that both arms of the model would have essentially the same chemotherapy costs, and accordingly did not include the cost of chemotherapy delivery in our model. All costs were adjusted to 2006 US dollars using the Medical Care Services component of the Consumer Price Index [27].

Pegfilgrastim cost was estimated at $2142 per injection per chemotherapy cycle (average of the 2006 average sales prices for quarters 1 to 4 [28]). The cost of administering pegfilgrastim was estimated to be $20/injection, obtained by averaging the fees associated with the Current Procedure Terminology (CPT) codes 99211 (Level One visit) and 90772 (Drug Administration) [29,30]. Patients receiving primary prophylaxis were assumed to be receiving one injection of pegfilgrastim in each cycle of chemotherapy. To estimate the cost of pegfilgrastim in patients receiving it for secondary prophylaxis after an FN event, we assumed that half of the patients who developed FN incurred it in the first cycle [6,31]. For FN events occurring after the first cycle, we assumed that the FN events were uniformly distributed across the remaining cycles.

Reported costs of FN hospitalization for breast cancer patients have ranged from $7100 to $12,372 [32–34]. We used the lower estimate, which was inflated to 2006 dollars using the medical care services component of the Consumer Price Index [27]. Because inpatient physician fees were not included in this estimate, we added 10% of the facility cost of FN hospitalization to account for physician services. The 10% physician fee was a conservative estimate based on a study on cardiovascular events and fractures among patients with end-stage renal disease, in which the authors reported that costs for physician services during the course of an inpatient stay were approximately 11% to 17% of the total cost [35]. Although the disease of interest is different between this study and ours, 10% for physician services in the United States may be a reasonable assumption. The cost of related health care after FN hospitalization was estimated to be 40% of the cost for initial FN hospitalization [20% because of rehospitalization(s) for FN, 20% because of ambulatory services] based on a study on lung cancer [11] and another that included 52% breast cancer patients [36]. The cost of outpatient FN management was assumed to be 50% of inpatient management. A recent study by Bennett et al. [37] reported that the mean direct cost was 3- to 10-fold greater for inpatients than for outpatients. Therefore, 10% was used for the lower bound in the sensitivity analysis on cost of outpatient FN management.

Clinical Parameters

The clinical parameters and ranges used in sensitivity analyses are summarized in Table 2. The risk of FN with secondary pegfilgrastim prophylaxis of 24.6%, which is also equivalent to that for no G-CSF, was based on a study by Martin et al. where patients receiving the TAC regimen initially were precluded from receiving G-CSF and experienced a high FN rate, and midway, they were changed to a protocol that required primary G-CSF support [31,38]. The FN relative risk reduction (RRR) of 73.58% for primary versus secondary prophylaxis (FN risk 6.5% vs. 24.6%) was based on the same study [31]. The range for FN RRR was varied from 46% [39] to 94% [6]. The FN risk was assumed to be modestly higher for patients aged 65 years and older (relative risk [RR] = 1.18) [40–42]. We estimated the risk of death in patients hospitalized with FN at 3.4% based on the results reported for breast cancer patients hospitalized with FN in two population-based studies [32,33]. The case fatality was assumed to be lower (0.5%) in patients eligible for

Table 2 Model inputs: clinical parameters

Parameter	Point estimate	Range
FN risk with secondary prophylaxis/no G-CSF	24.6% [31,38]	20%, 40%
FN RRR: primary vs. secondary prophylaxis	73.58% [31]	46%, 94% [6,39]
FN risk with primary prophylaxis	6.5% [31,77]	Vary depending on the two variables above
FN case fatality (% death among hospitalized FN patients)	3.4% [32]	0%, 7% [8,32,33,78]
FN case fatality (% death among FN patients managed at outpatient settings)	0.5% [43–45]	
Utility scores for breast cancer during chemotherapy	0.70 [79]	
Utility scores for FN hospitalization	0.33*	0.24, 0.42 [66,80]
Utility scores for breast cancer in years 1–5	0.86 [81]	0.30, 0.90
Utility scores for breast cancer in years after year 5	0.96 [82]	0.50, 1.00

*Median of reported range.
BR, baseline risk; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; OR, odds ratio; RDI, relative dose intensity; RR, relative risk; RRR, relative risk reduction.

outpatient management of FN based on studies that reported mortality rates of 0% to 2% in various cancer types [43–46].

Breast cancer mortality by stage and year since diagnosis were obtained from the Surveillance Epidemiology and End Results (SEER) database [47]. All-cause mortality data were obtained from National Vital Statistics Reports [48] and were adjusted to account for deaths because of breast cancer [49].

Health Utilities

Health utility scores, which are numerical judgments (0 = death, 1 = ideal health) of the desirability of a particular health outcome, were used to calculate quality-adjusted life-years (QALY). Utility scores for the following health states were obtained from the literature: breast cancer during chemotherapy, FN, breast cancer survivor during years 1 to 5 following treatment, and breast cancer survivor more than 5 years after treatment (Table 2).

Analyses

Costs, FN events, average life expectancy, and average quality-adjusted life expectancy were estimated for primary prophylaxis versus secondary prophylaxis. Incremental cost-effectiveness ratios (ICERs) were calculated: cost/FN event avoided, cost/life-year gained (LYG), and cost/QALY gained. Because no costs of interest to this study were modeled beyond 1 year, only future effectiveness measures such as LYG and QALY saved were discounted, using a discount rate of 3% per annum in the base case [50].

Two scenarios were analyzed in the model. Scenario 1 considered only the effect of G-CSF on the incidence and cost of FN (i.e., assuming G-CSF has no impact on short- or long-term mortality). Scenario 2 estimated cost/LYG ($/LYG) and cost/QALY gained ($/QALY gained) under the assumption that G-CSF also influences FN-related mortality.

One-way sensitivity analyses were conducted (scenario 2) on key variables, including FN risks (baseline and RR), FN case-fatality, RDI-related parameters, cost of drugs, and utility scores. We performed a sensitivity analysis related to the effect of prophylaxis on the likelihood of receiving an adequate dose of chemotherapy (RDI) and the impact of RDI < 85% on survival. This analysis was performed as an extension to the model, with branches after chemotherapy indicating the probabilities that the patient received <85% or ≥85% of the RDI and their subsequent impact on long-term survival. The baseline (secondary prophylaxis) RDI <85% was estimated to be 18.5% regardless of RR of RDI <85% used [51], although it could be up to 55.5% [52–55]. The RR of receiving <85% RDI between primary versus secondary prophylaxis was based on a recent meta-analysis of G-CSF primary prophylaxis trials [39], which reported mean chemotherapy RDI of 95.1% and 86.7% for patients in the primary prophylaxis arms versus the control arms of the trials, respectively. G-CSF was used after an FN event in the control arms (i.e., secondary prophylaxis) in only 3 out of the 17 trials included in this meta-analysis. Assuming a normal distribution, the estimated probabilities of receiving <85% of RDI in the primary prophylaxis and control arms were calculated at 40.2% and 47.0%, respectively, resulting in an RR of 0.86. In addition, the cancer types included in these trials were solid tumors and aggressive non-Hodgkin's lymphoma, while our model is for patients with breast cancer. Despite this imperfect information, we included in the sensitivity analysis the RR of RDI < 85% of 0.86—1 for primary versus secondary prophylaxis to account for the potential survival benefit. The impact of reduced chemotherapy RDI was assumed to increase the risk of long-term cancer-specific mortality by 1.32 based on a long-term follow-up study of clinical trials [56] and recent observational studies [51,57–59]. The risk of receiving <85% RDI was assumed to be higher for patients ≥65 years compared with younger patients (RR = 1.33) regardless of receipt of G-CSF prophylaxis [40,42,55,60].

Probabilistic sensitivity analyses were performed on the following parameters with respective distributions: age and cancer stage (distribution data were from SEER [47]), FN case-fatality (assumed triangular distribution), FN RRR for primary versus secondary prophylaxis (assumed triangular distribution), baseline FN risk (assumed triangular distribution), and cost of initial FN hospitalization (assumed log normal distribution with a median of $4000 [32,33] and mean of $9745 [32]). For a triangular distribution, the likeliest value was the point estimate, and the minimum and maximum values were the lower and upper bound of the range for each variable, respectively (Tables 1 and 2). The results were plotted on a cost-effectiveness acceptability curve for scenario 2, which shows the probability that primary prophylaxis is cost-effective as a function of a payer's willingness to pay (WTP) for a unit of health benefit.

Results

Two Scenarios (Table 3)

Primary prophylaxis cost $8703 more per patient than secondary prophylaxis ($13,791 versus $5,088). In scenario 1, the ICER of pegfilgrastim primary versus secondary prophylaxis was approximately $48,000/FN episode avoided. When the survival effects associated with avoiding FN-related mortality were included (scenario 2), the resulting average life expectancy for primary versus secondary prophylaxis was 15.701 years versus 15.622 years, respectively, yielding an ICER of $110,000/LYG [95% confidence interval (CI): $84K/LYG–$136K/LYG]. The ICER from the cost-utility analysis was $116,000/QALY gained (95% CI: $97K/QALY–$135K/QALY).

Table 3 Cost-effectiveness of pegfilgrastim as primary versus secondary prophylaxis against febrile neutropenia (FN) for women receiving TAC regimen

		Scenario 1	Scenario 2 (95% credibility interval)	
	Cost ($)	Risk of FN	LY	QALY
Secondary prophylaxis	5,088	24.6%	15.622	14.487
Primary prophylaxis	13,791	6.5%	15.701	14.563
ICER	—	$48K/FN event avoided	$110K/LYG ($84K/LYG–$136K/LYG)	$116K/QALY ($97K/QALY–$135K/QALY)

Scenario 1: pegfilgrastim only impacts the frequency of FN but has no influence on FN mortality, or RDI and its long-term survival benefit. Scenario 2: pegfilgrastim impacts the frequency of FN and the mortality associated with those events, but has no influence on RDI and its long-term survival benefit.
ICER, incremental cost-effectiveness ratio; K, 1000; LY, life-year; LYG, life-years gained; QALY, quality-adjusted life-years; TAC, docetaxel, doxorubicin/docetaxel, or docetaxel/doxorubicin/cyclophosphamide.

One-Way Sensitivity Analyses

In one-way sensitivity analyses using scenario 2 as the reference case, the results were sensitive (in order) to the following variables: FN case-fatality, FN RRR, age at breast cancer diagnosis, baseline FN risk without primary G-CSF prophylaxis, pegfilgrastim cost, cancer stage, utility scores after year 5, cost of initial FN hospitalization, number of chemotherapy cycles, RR of chemotherapy RDI < 85% for primary versus secondary prophylaxis, proportion of FN treated at outpatient settings, discount rate, and utility score for the first year post-chemotherapy and years 2–5. Results were less sensitive (or not sensitive at all) to other variables, including subsequent FN-related care cost, cost of administering pegfilgrastim, proportion of FN events that occurred in the first cycle, outpatient cost, physician fee, and utility scores for chemotherapy treatment and FN hospitalization (Fig. 2). When FN case fatality was <2%, the ICER exceeded $200,000/QALY gained. When varying all other variables within the specified ranges, the ICER did not exceed $200,000/QALY gained except for when the age at diagnosis was near 80 years. The ICER was $156,000/QALY for baseline risk of FN at 20%, and $49,000/QALY for baseline risk of FN at 40%. When adding the potential long-term survival benefit of pegfilgrastim associated with achieving optimal chemotherapy dose intensity to the benefits of avoiding FN-related mortality (RR of RDI <85% was 0.86), the ICER was $74,000/QALY gained.

Probabilistic Sensitivity Analyses

In the probabilistic sensitivity analysis for scenario 2, the probability that pegfilgrastim primary prophylaxis would be considered cost-effective at the threshold value compared with secondary prophylaxis was 12% for a WTP of $50,000/QALY gained, 40% for a WTP of $100,000/QALY gained, and 75% for a WTP of $200,000/QALY gained (Fig. 3).

Discussion

Using simulation modeling, we evaluated the cost-effectiveness of pegfilgrastim as primary versus secondary prophylaxis for women with breast cancer receiving chemotherapy that carries an FN risk of approximately 20% or higher. This is the first analysis of primary prophylaxis with G-CSF to consider FN-related survival benefits and potential long-term survival benefits because of maintaining chemotherapy dose intensity. Prior economic assessments of G-CSF were primarily cost-minimization studies [11–13,61,62] that assumed no difference in clinical outcomes that influence patient survival or quality of life. These studies estimated that G-CSF ranged from being cost-saving [12,13] to costing $48,000 (£37,000) per FN event avoided [11]. A modeling study by Silber et al. [63] also simulated patients undergoing adjuvant chemotherapy; however, they considered the cost-effectiveness of using G-CSF starting in cycle 2 in patients with breast cancer considered at high risk based on their response to chemotherapy in the first cycle, not primary prophylaxis in cycle 1 as is currently recommended by clinical guidelines. Because of the hierarchy of evidence G-CSF use FN-related mortality, and a direct link between G-CSF use and long-term cancer-related survival, we considered two scenarios in the core model. Scenario 1 was supported by the strongest evidence, in which we considered

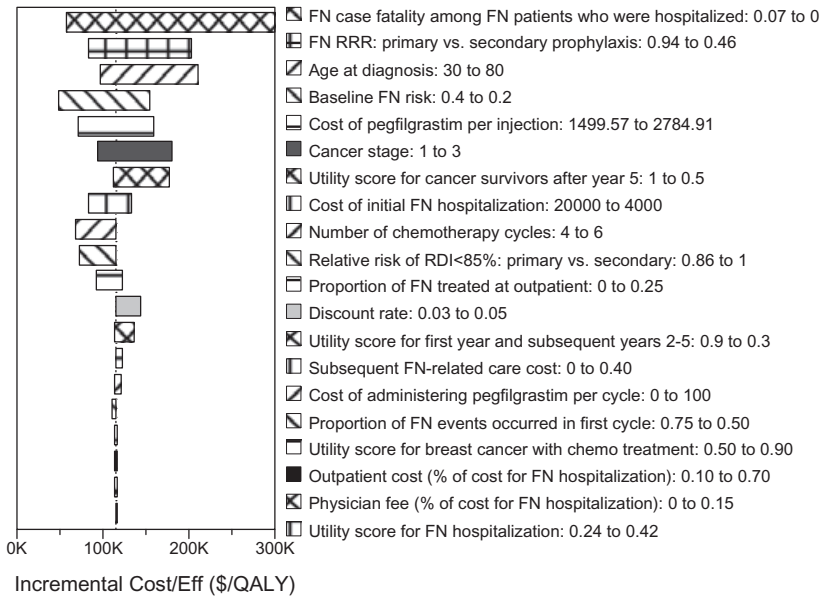

Figure 2 Tornado diagram showing results of one-way sensitivity analysis for scenario 2: primary versus secondary prophylaxis with pegfilgrastim. Top bar was right truncated. FN, febrile neutropenia; QALY, quality-adjusted life-year; RDI, relative dose intensity; RRR, relative risk reduction.

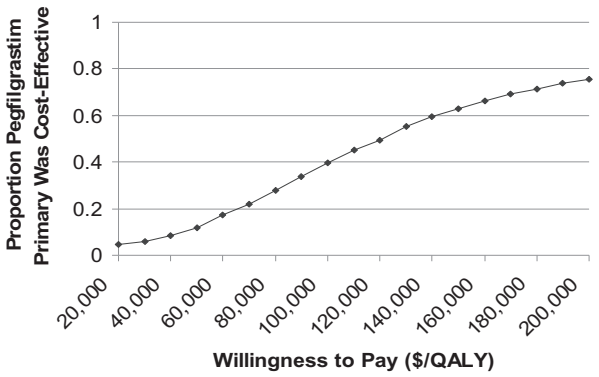

Figure 3 Acceptability curve for pegfilgrastim primary versus secondary prophylaxis. QALY, quality-adjusted life-year.

only the effect of G-CSF on the incidence and cost of FN and assumed that G-CSF has no impact on near- or long-term mortality, and scenario 2 was supported by moderate evidence, in which we assumed that primary prophylaxis reduced short-term FN mortality. In the sensitivity analysis, we considered the enhanced long-term survival by increasing the likelihood that patients will receive the full planned chemotherapy dose.

The cost-effectiveness of pegfilgrastim prophylaxis at $116,000/QALY in scenario 2 (assuming G-CSF impacts the frequency of FN and the mortality associated with those events, but has no influence on RDI and its long-term survival benefit) is less favorable than many health-care interventions, but compares favorably with other supportive care therapies in cancer, including pamidronate for preventing skeletal events in patients with bone metastases ($108,200–$305,300/QALY) [64] and ondansetron for cisplatin-induced emesis ($190,000/QALY to $460,000/QALY) [65]. The cost-effectiveness of pegfilgrastim primary prophylaxis is less favorable than the addition of taxanes to adjuvant chemotherapy regimens ($27,000/QALY) [66,67], but similar to trastuzumab for treatment of metastatic breast cancer ($125,100/QALY) [68], both considered standards of care. Using the most conservative scenario (i.e., scenario 1), pegfilgrastim as primary prophylaxis would be considered cost-effective for decision-makers if they were willing to pay $48,000 or more to avoid an FN event.

The primary limitations of our analysis are the lack of direct evidence linking G-CSF use with a reduction of FN-related mortality and improvements in long-term cancer-specific survival. Although individual trials were not designed to assess the impact of G-CSF on neutropenia-related mortality, a recent meta-analysis of 12 randomized controlled clinical trials found that patients receiving G-CSF were less likely to die of infectious complications (1.5%) compared with control subjects (2.8%; $P = 0.018$). Similarly, G-CSF has not been shown to improve cancer outcomes by allowing chemotherapy to be delivered at planned dose intensity. The aforementioned meta-analysis found that among trials reporting chemotherapy dose intensity (1942 patients), the average dose intensity was 86.7% for controls versus 95.1% for patients receiving G-CSF ($P = 0.001$) [39]. Although observational studies suggest that patients with breast cancer who receive chemotherapy doses consistent with those demonstrated to be effective in clinical trials have lower relapse rates and improved overall survival [51,56–59], further research is needed to establish the RDI of chemotherapy needed to assure optimal outcomes. For patients at a moderate risk of FN, including these additional health benefits in the model had a modest impact on the cost-effectiveness of G-CSF (i.e., the ICER could be reduced to $74,000/QALY gained).

This analysis was limited to pegfilgrastim and did not consider other G-CSFs recommended in the guidelines, namely filgrastim (Neupogen, Amgen Inc. Thousand Oaks, CA) and sargramostim (Leukine; Bayer HealthCare Pharmaceuticals, Wayne, NJ). Although sargramostim has been available since 1991 [69], its use in this setting has been limited by a paucity of data demonstrating efficacy in reducing FN in patients receiving myelosuppressive chemotherapy and the absence of an approved indication [70–72]. Filgrastim should have similar to or worse cost-effectiveness than pegfilgrastim primary prophylaxis because of its comparable or more expensive cost [4,5,73] and comparable or worse efficacy in reducing FN rates [74]. A recent study showed that prophylactic administration of pegfilgrastim was cost saving compared to both filgrastim and no G-CSF [75]. When biosimilar filgrastim becomes available, it would be reasonable to compare its costs and effects with those of pegfilgrastim.

Our analysis considers the health payer's perspective, whereas a societal perspective may be important in other circumstances [76]. Including indirect costs such as patient time, caregiver costs, and lost productivity may improve the cost-effectiveness of primary prophylaxis because of primary prophylaxis' beneficial impact on FN-related morbidity and short-term and long-term mortality.

Lastly, our model excluded the cost of chemotherapy. The costs of chemotherapy depend on the number of chemotherapy cycles received. If a patient dies from an FN event during chemotherapy, presumably no further costs would be incurred after the patient died. Excluding the cost of chemotherapy thus biased the results against G-CSF secondary prophylaxis (as chemotherapy costs are saved when patients die from FN events). Nevertheless, because the overall mortality because of FN was very low, eliminating this bias is unlikely to have a meaningful impact on the results and conclusions.

Myeloid growth factor guidelines published by the ASCO, NCCN, and EORTC support the use of primary prophylaxis in patients receiving chemotherapy regimens associated with a risk of FN of 20% or higher [1,7,8]. The risk of FN associated with particular chemotherapy regimens is based on data reported by randomized controlled trials, which typically include highly selected patient populations. For this reason, these guidelines also advise consideration of additional risk factors in estimating a patient's individual FN risk. Our model does not account for factors other than chemotherapy and age that might influence a patient's risk for FN. Retrospective studies find that much of the G-CSF treatment in the community is given as secondary prophylaxis [9]. Programs for changing practice to providing G-CSFs as primary prophylaxis in appropriate patients would likely improve FN-related patient outcomes. Our study suggests that for women with breast cancer undergoing chemotherapy with moderate myelosuppressive risk, such programs may also be cost-effective if program costs are modest and result in significant changes in prescribing patterns. Further assessments of the direct impact of G-CSFs on both short-term and long-term survival are needed to substantiate our findings.

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Supporting information for this article can be found at [1S]: http://www.ispor.org/publications/value/ViHsupplementary.asp.

1S Lyman GH, Kuderer NM, Crawford J, et al. Prophylactic granulocyte colony-stimulating factor (G-CSF) in cancer patients receiving

chemotherapy: a metaanalysis (abstract 07-059). Presented at the 17th Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology International Symposium, Geneva, Switzerland, July 2, 2005.

References

1 Smith TC, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006; 24:3187–205.
2 Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325:164–70.
3 Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer 1993;29A: 319–24.
4 Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002;20:727–31.
5 Green MD, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003;14:29–35.
6 Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 2005;23:1178–84.
7 Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 2006; 42:2433–53.
8 Lyman GH. Guidelines of the National Comprehensive Cancer Network on the use of myeloid growth factors with cancer chemotherapy: a review of the evidence. J Natl Compr Canc Netw 2005;3:557–71.
9 Bennett CL, Weeks JA, Somerfield MR, et al. Use of hematopoietic colony-stimulating factors: comparison of the 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines. Health Services Research Committee of the American Society of Clinical Oncology. J Clin Oncol 1999;17:3676–81.
10 Crawford J, Althaus B, Armitage J, et al. Myeloid growth factors clinical practice guidelines in oncology. J Natl Compr Canc Netw 2005;3:540–55.
11 Timmer-Bonte JN, Adang EM, Smit HJ, et al. Cost-effectiveness of adding granulocyte colony-stimulating factor to primary prophylaxis with antibiotics in patients with small-cell lung cancer. J Clin Oncol 2006;24:2991–7.
12 Lyman GH, Lyman CG, Sanderson RA, Balducci L. Decision analysis of hematopoietic growth factor use in patients receiving cancer chemotherapy. J Natl Cancer Inst 1993;85:488–93.
13 Lyman GH, Kuderer N, Greene J, Balducci L. The economics of febrile neutropenia: implications for the use of colony-stimulating factors. Eur J Cancer 1998;34:1857–64.
14 Cosler LE, Calhoun EA, Agboola O, Lyman GH. Effects of indirect and additional direct costs on the risk threshold for prophylaxis with colony-stimulating factors in patients at risk for severe neutropenia from cancer chemotherapy. Pharmacotherapy 2004; 24:488–94.
15 Cosler LE, Sivasubramaniam V, Agboola O, et al. Effect of outpatient treatment of febrile neutropenia on the risk threshold for the use of CSF in patients with cancer treated with chemotherapy. Value Health 2005;8:47–52.
16 Uyl-de Groot CA, Vellenga E, Rutten FF. An economic model to assess the savings from a clinical application of haematopoietic growth factors. Eur J Cancer 1996;32A:57–62.
17 Glaspy JA, Bleecker G, Crawford J, et al. The impact of therapy with filgrastim (recombinant granulocyte colony-stimulating factor) on the health care costs associated with cancer chemotherapy. Eur J Cancer 1993;29(Suppl. 7):S23–30.
18 Dranitsaris G, Altmayer C, Quirt I. Cost-benefit analysis of prophylactic granulocyte colony-stimulating factor during CHOP antineoplastic therapy for non-Hodgkin's lymphoma. Pharmacoeconomics 1997;11:566–77.
19 Dranitsaris G, Sutcliffe SB. Economic analysis of prophylactic G-CSF after mini-BEAM salvage chemotherapy for Hodgkin's and non-Hodgkin's lymphoma. Leuk Lymphoma 1995;17:139–45.
20 Talcott JA. Out-patient management of febrile neutropenia. Int J Antimicrob Agents 2000;16:169–71.
21 Doorduijn JK, Buijt I, van der HB, et al. Economic evaluation of prophylactic granulocyte colony stimulating factor during chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma. Haematologica 2004;89:1109–17.
22 Peroutka JA, Mutnick AH. Use of decision analysis to evaluate the costs and benefits of filgrastim (G-CSF) therapy. Formulary 1995;30:394.
23 Nichols CR, Fox EP, Roth BJ, et al. Incidence of neutropenic fever in patients treated with standard-dose combination chemotherapy for small-cell lung cancer and the cost impact of treatment with granulocyte colony-stimulating factor. J Clin Oncol 1994;12:1245–50.
24 Lyman GH, Dale DC, Friedberg J, et al. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol 2004;22:4302–11.
25 Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. J Clin Oncol 1992;10:316–22.
26 Klastersky J, Paesmans M, Rubenstein EB, et al. The multinational association for supportive care in cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18:3038–51.
27 US Department of Labor. Bureau of labor statistics. Updated 2006. Available from: http://www.bls.gov/cpi/home.htm#overview. [Accessed February 23, 2007].
28 Centers for Medicare and Medicaid Services. Medicare Part B Drug Average Sales Price 2006 ASP drug pricing files. Updated 2007. Available from: http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/02_aspfiles.asp [Accessed March 18, 2008].
29 American Medical Society. Current Procedural Terminology (CPT). CPT 99211, CPT 90772. Chicago, IL: American Medical Association, 2006.
30 Centers for Medicare and Medicaid Services. 2006 Medicare physician fee schedule. Updated 2006. Available from: http://www.cms.hhs.gov/PFSlookup/ [Accessed March 18, 2008].
31 Martin M, Lluch A, Segui MA, et al. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. Ann Oncol 2006;17:1205–12.
32 Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble. WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer 2005;103:1916–24.
33 Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258–66.
34 Liou SY, Stephens JM, Carpiuc KT, et al. Economic burden of haematological adverse effects in cancer patients: a systematic review. Clin Drug Investig 2007;27:381–96.
35 Doan QV, Gleeson M, Kim J, et al. Economic burden of cardiovascular events and fractures among patients with end-stage renal disease. Curr Med Res Opin 2007;23:1561–9.
36 Weycker D, Malin J, Edelsberg J, et al. Cost of neutropenic complications of chemotherapy. Ann Oncol 2008;19:454–60.

37 Bennett CL, Calhoun EA. Evaluating the total costs of chemotherapy-induced febrile neutropenia: results from a pilot study with community oncology cancer patients. Oncologist 2007;12:478–83.
38 Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302–13.
39 Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007; 25:3158–67.
40 Lyman GH, Crawford J. Dale D, for the ANC study group. Clinical prediction models for febrile neutropenia (FN) and relative dose intensity (RDI) in patients receiving adjuvant breast cancer chemotherapy. Proc Am Soc Clin Oncol 2001;20:394A.
41 Weycker D, Hackett J, Edelsberg JS, et al. Are shorter courses of filgrastim prophylaxis associated with increased risk of hospitalization? Ann Pharmacother 2006;40:402–7.
42 Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. Oncologist 2005;10:427–37.
43 Klastersky J, Paesmans M, Georgala A, et al. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. J Clin Oncol 2006;24:4129–34.
44 Chamilos G, Bamias A, Efstathiou E, et al. Outpatient treatment of low-risk neutropenic fever in cancer patients using oral moxifloxacin. Cancer 2005;103:2629–35.
45 Uys A, Rapoport BL, Anderson R. Febrile neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. Support Care Cancer 2004;12:555–60.
46 Klastersky J, Paesmans M. Risk-adapted strategy for the management of febrile neutropenia in cancer patients. Support Care Cancer 2007;15:477–82.
47 Surveillance, Epidemiology, and End Results (SEER) program SEER*stat database: Incidence–Seer 9 regs public-use, Nov 2004 Sub (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission. Updated April 2005. Available from: http://www.seer.cancer.gov [Accessed November 16, 2007].
48 Life table for females: United States. National Vital Statistics Reports, 53, 6, November 10, 2004, Table 3. Updated 2002. Available from: http://www.cdc.gov/nchs/data/nvsr/nvsr53/nvsr 53_06.pdf [Accessed February 23, 2007].
49 United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. Compressed Mortality File (CMF) compiled from CMF 1999–2002, Series 20, No. 2H 2004 on CDC WONDER. Available from http://wonder.cdc.gov/cmf-icd10.htm [Accessed July 11, 2008].
50 Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the panel on cost-effectiveness in health and medicine. JAMA 1996;276:1253–8.
51 Colleoni M, Li S, Gelber RD, et al. Relation between chemotherapy dose, oestrogen receptor expression, and body-mass index. Lancet 2005;366:1108–10.
52 Morrow T, Siegel M, Boone S, et al. Chemotherapy dose intensity determination as a quality of care measure for managed care organizations in the treatment of early-stage breast cancer. Am J Med Qual 2002;17:218–24.
53 Leonard RC, Miles D, Thomas R, Nussey F. Impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. Br J Cancer 2003;89:2062–8.
54 Link BK, Budd GT, Scott S, et al. Delivering adjuvant chemotherapy to women with early-stage breast carcinoma: current patterns of care. Cancer 2001;92:1354–67.
55 Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 2003; 21:4524–31.
56 Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. BMJ 2005;330:217.
57 Bonadonna G, Valagussa P, Moliterni A, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med 1995;332:901–6.
58 Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med 1981;304:10–5.
59 Hershman D, McBride R, Jacobson JS, et al. Racial disparities in treatment and survival among women with early-stage breast cancer. J Clin Oncol 2005;23:6639–46.
60 Shayne M, Crawford J, Dale DC, et al. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. Breast Cancer Res Treat 2006;100:255–62.
61 Lyman GH, Kuderer NM. Cost effectiveness of myeloid growth factors in cancer chemotherapy. Curr Hematol Rep 2003;2: 471–9.
62 Lyman GH, Kuderer NM. Economics of hematopoietic growth factors. In: Morstyn G, Foote M, Lieschke GJ, eds. Hematopoietic Growth Factors in Oncology: Basic Science and Clinical Therapeutics. Totowa, NJ: Humana Press, 2004.
63 Silber JH, Fridman M, Shpilsky A, et al. Modeling the cost-effectiveness of granulocyte colony-stimulating factor use in early-stage breast cancer. J Clin Oncol 1998;16:2435–44.
64 Hillner BE, Weeks JC, Desch CE, Smith TJ. Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis. J Clin Oncol 2000;18:72–9.
65 Zbrozek AS, Cantor SB, Cardenas MP, et al. Pharmacoeconomic analysis of ondansetron versus metoclopramide for cisplatin-induced nausea and vomiting. Am J Hosp Pharm 1994;51:1555–63.
66 Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. Pharmacoeconomics 2001;19:1091–102.
67 Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J. A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer. Health Technol Assess 2000;4:1–113.
68 Elkin EB, Weinstein MC, Winer EP, et al. HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. J Clin Oncol 2004;22:854–63.
69 Drugs@FDA. FDA approved drug products. Updated 2007. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails [Accessed June 1, 2007].
70 Wong SF, Chan HO. Effects of a formulary change from granulocyte colony-stimulating factor to granulocyte-macrophage colony-stimulating factor on outcomes in patients treated with myelosuppressive chemotherapy. Pharmacotherapy 2005;25: 372–8.
71 Steward WP, Von Pawel J, Gatzemeier U, et al. Effects of granulocyte-macrophage colony-stimulating factor and dose intensification of V-ICE chemotherapy in small-cell lung cancer: a prospective randomized study of 300 patients. J Clin Oncol 1998;16:642–50.
72 Yau JC, Neidhart JA, Triozzi P, et al. Randomized placebo-controlled trial of granulocyte-macrophage colony-stimulating-factor support for dose-intensive cyclophosphamide, etoposide, and cisplatin. Am J Hematol 1996;51:289–95.
73 Holmes FA, Jones SE, O'Shaughnessy J, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. Ann Oncol 2002;13:903–9.
74 Siena S, Piccart MJ, Holmes FA, et al. A combined analysis of two pivotal randomized trials of a single dose of pegfilgrastim per chemotherapy cycle and daily Filgrastim in patients with stage II-IV breast cancer. Oncol Rep 2003;10:715–24.
75 Eldar-Lissai A, Cosler LE, Culakova E, Lyman GH. Economic analysis of prophylactic pegfilgrastim in adult cancer patients receiving chemotherapy. Value Health 2008;11:172–9.

76 Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the panel on cost-effectiveness in health and medicine. JAMA 1996;276:1253–8.
77 von Minckwitz G, Kummel S, du Bois A, et al. Pegfilgrastim {+/–} ciprofloxacin for primary prophylaxis with TAC (docetaxel/doxorubicin/cyclophosphamide) chemotherapy for breast cancer. Results from the GEPARTRIO study. Ann Oncol 2008;19:292–8.
78 Lyman GH, Kuderer NM. The economics of the colony-stimulating factors in the prevention and treatment of febrile neutropenia. Crit Rev Oncol Hematol 2004;50:129–46.
79 Hillner BE, Smith TJ, Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results. JAMA 1992;267:2055–61.
80 Brown RE, Hutton J. Cost-utility model comparing docetaxel and paclitaxel in advanced breast cancer patients. Anticancer Drugs 1998;9:899–907.
81 Armstrong K, Chen TM, Albert D, et al. Cost-effectiveness of raloxifene and hormone replacement therapy in postmenopausal women: impact of breast cancer risk. Obstet Gynecol 2001;98:996–1003.
82 Liljegren G, Karlsson G, Bergh J, Holmberg L. The cost-effectiveness of routine postoperative radiotherapy after sector resection and axillary dissection for breast cancer stage I. Results from a randomized trial. Ann Oncol 1997;8:757–63.