**DOI:**10.1093/jnci/djt182
Advance Access publication July 19, 2013


ARTICLE

# Cost-Effectiveness of Filgrastim and Pegfilgrastim as Primary Prophylaxis Against Febrile Neutropenia in Lymphoma Patients

Nina Lathia, Pierre K. Isogai, Carlo De Angelis, Thomas J. Smith, Matthew Cheung, Nicole Mittmann, Jeffrey S. Hoch, Scott Walker

Manuscript received December 19, 2012; revised April 23, 2013; accepted April 25, 2013.

**Correspondence to:** Nina Lathia, RPh MSc, Rm E300, 2075 Bayview Ave, Toronto, ON M4N 3M5, Canada (e-mail: nina.lathia@sunnybrook.ca).

**Background** Febrile neutropenia is a serious toxicity of cancer chemotherapy that is usually treated in hospital. We assessed the cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia in diffuse large B-cell lymphoma (DLBCL) patients undergoing chemotherapy.

**Methods** We used a Markov model that followed patients through induction chemotherapy to compare the three prophylaxis strategies: 1) no primary prophylaxis against febrile neutropenia; 2) primary prophylaxis with 10 days of filgrastim therapy; and 3) primary prophylaxis with a single dose of pegfilgrastim. The target population was a hypothetical cohort of 64-year-old men and women with DLBCL. Data sources included published literature and current clinical practice. The analysis was conducted from a publicly funded health-care system perspective. The main outcome measures included costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs).

**Results** In the base-case analysis, costs associated with no primary prophylaxis, primary prophylaxis with 10 days of filgrastim, and primary prophylaxis with pegfilgrastim were CaD $7314, CaD $13947, and CaD $16290, respectively. The QALYs associated with the three strategies were 0.2004, 0.2015, and 0.2024, respectively. The ICER for the filgrastim vs no primary prophylaxis strategy was CaD $5796000 per QALY. The ICER for the pegfilgrastim vs filgrastim primary prophylaxis strategy was CaD $2611000 per QALY. All one-way sensitivity analyses yielded ICERs greater than CaD $400000 per QALY. Cost-effectiveness acceptability curves show that 20.0% of iterations are cost-effective at a willingness-to-pay threshold of CaD $1595000 for the filgrastim strategy and CaD $561000 for the pegfilgrastim strategy.

**Conclusions** Primary prophylaxis against febrile neutropenia with either filgrastim or pegfilgrastim is not cost-effective in DLBCL patients.

J Natl Cancer Inst;2013;105:1078–1085



Non-Hodgkin lymphoma is the seventh most common malignancy in the United States (1); its incidence has increased by about 20% since 1987 (2). Diffuse large B-cell lymphoma (DLBCL) is the most common Non-Hodgkin lymphoma subtype, accounting for approximately 25% of cases (3). Initial standard treatment for DLBCL includes combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) (4). This regimen yields 5- and 10-year survival rates of 51% and 45%, respectively (5,6). Febrile neutropenia is a serious toxicity of R-CHOP chemotherapy and is typically treated in hospital with antibiotics (7). Clinical trials have shown that up to 50% of patients who receive R-CHOP experience febrile neutropenia (8,9).

There are two granulocyte-colony stimulating factors (G-CSFs), filgrastim and pegfilgrastim, currently available that are efficacious in preventing febrile neutropenia (10). The American Society of Clinical Oncology recommends using G-CSFs with chemotherapy regimens associated with a 20% or greater incidence of febrile neutropenia. They also specifically recommend G-CSF support for all Non-Hodgkin lymphoma patients aged greater than 65 years who are receiving CHOP-based chemotherapy because the risk of neutropenia increases with age. The authors of these guidelines state that their recommendations were based on clinical, not economic, evidence and note that further research on cost implications of G-CSF use is needed (11).

Although several cost-effectiveness analyses evaluating pegfilgrastim have been published recently (12–18), all of them assumed a mortality benefit associated with G-CSF use despite the fact that randomized trials in lymphoma patients have not demonstrated a survival benefit (19–21). One recently published cost-effectiveness analysis did not assume a mortality benefit with G-CSF use but evaluated only filgrastim (22).

The objective of this study was to determine whether primary prophylaxis against febrile neutropenia using either filgrastim or pegfilgrastim in DLBCL patients undergoing R-CHOP chemotherapy is cost-effective from the perspective of the publicly

funded health-care system in Ontario, Canada. We conducted a cost-effectiveness analysis to estimate the incremental cost-effectiveness ratios (ICERs) of filgrastim and pegfilgratim primary prophylaxis in this population.

## Methods

We estimated the health benefits and costs of using filgrastim and pegfilgrastim compared with no primary prophylaxis against febrile neutropenia in DLBCL patients undergoing chemotherapy. Recommendations for conducting and reporting cost-effectiveness analyses by Philips et al. were followed (23).

### Model Cohort, Health States, and Costs

We constructed a Markov model that followed a cohort of patients over the course of their initial chemotherapy using the R language and environment for statistical computing (R Foundation for Statistical Computing), version 2.14.1 (http://www.r-project.org/). DLBCL patients receiving induction chemotherapy with R-CHOP were evaluated in this analysis. The base-case analysis considered a cohort of 64-year-old men and women, reflecting the median age of diagnosis (3). Equal proportions of patients in all International Prognostic Index categories were included. This index is used to predict long-term survival of DLBCL patients; scores range from zero to five, with lower scores representing a greater chance of survival (24).

Costs and health utilities associated with chemotherapy-induced febrile neutropenia and no febrile neutropenia while receiving chemotherapy were included in the model. No other health states were incorporated into the model for several reasons. First, several studies have demonstrated that relapse-free survival and overall survival rates are no different between lymphoma patients who receive G-CSF support and those who do not (19–21). Furthermore, three large meta-analyses have demonstrated no mortality benefit with G-CSF use: one meta-analysis combined data from more than 2 000 patients from 13 trials done in lymphoma patients and found that G-CSF provided no statistically significant benefit in overall survival (25); another meta-analysis combined data from more than 12 000 patients from 148 trials of patients with various malignancies and found no statistically significant decrease in all-cause mortality for patients who received G-CSFs (26); and finally, another meta-analysis combined data from more than 12 000 patients from 25 trials done in patients with various malignancies and found that a reduction in overall mortality was only observed with dose-intense chemotherapy and not with standard-dose chemotherapy (27). Second, no fatalities as a result of filgrastim or pegfilgrastim have occurred (19,21). Third, the only reported adverse effect of G-CSF was musculoskeletal pain in less than 10% of patients, which was treated with simple analgesics and did not lead to any discontinuation of therapy (20,21). Fourth, there was no difference in chemotherapy-related adverse events between patients who received G-CSF and those who did not (21). Finally, reducing chemotherapy doses or delaying its administration after febrile neutropenia did lead to statistically significantly lower relative dose intensities but not to an overall lower complete response rate or worse overall survival (19,20).

A cycle length of 3 weeks was used, representing the time between chemotherapy cycles. The time horizon of the model was 18 weeks, the period over which the six chemotherapy cycles are administered. A lifetime time horizon was not used because G-CSFs are solely supportive care therapies that have no effects, either beneficial or adverse, after chemotherapy (10,26). Health outcomes are reported in quality-adjusted life days (QALDs) as well as quality-adjusted life years (QALYs) because of the model's short time horizon.

Costs were considered from the Ontario Ministry of Health and Long-Term Care perspective, the government ministry responsible for public funding of health care in Ontario, and are reported in 2012 Canadian dollars. No discounting was applied because the model time horizon was less than 1 year.

### Data Sources

Estimates of costs, health utility values, and probabilities were based on published sources where possible. Table 1 outlines the parameter values used and their sources.

### Probabilities

We identified four published meta-analyses that examined the effectiveness of G-CSF (10,25,26,35). The results of these studies, however, were not used in this analysis because three of them included studies of patients with both solid tumors and hematologic malignancies, and they all included studies that examined the effectiveness of not only filgrastim but also lenograstim and pegfilgrastim. We conducted a separate meta-analysis to estimate the probability of experiencing a febrile neutropenia episode in lymphoma patients when receiving primary prophylaxis with filgrastim. The Supplementary Materials (available online) detail the methods and results of this meta-analysis (see Supplementary Table 1 and Supplementary Figure 1, available online). No meta-analysis of pegfilgrastim studies was done because only one study examined its efficacy in lymphoma patients (32).

### Febrile Neutropenia

We assumed that patients who developed febrile neutropenia did so on day 7 postchemotherapy, coinciding with the nadir in absolute neutrophil count (34). Although some evidence suggests that the risk of febrile neutropenia is increased in patients who have experienced a previous episode, it is inconclusive (36). For this analysis, we assumed that the risk of experiencing febrile neutropenia remained constant over all six chemotherapy cycles. Patients in the filgrastim primary prophylaxis arm received 300 μg of filgrastim for 10 days after each chemotherapy cycle. Patients in the pegfilgrastim arm received a single 6-mg dose. We assumed that patients in the no primary prophylaxis arm who experienced a febrile neutropenia episode would receive secondary prophylaxis with filgrastim 300 μg once daily for 10 days with all subsequent chemotherapy cycles, which reflects current clinical practice, regardless of whether febrile neutropenia risk is increased or not with downstream cycles (37).

In the base-case analysis, we assumed that all patients would be hospitalized for febrile neutropenia. However, studies show that lymphoma patients at low risk for febrile neutropenia complications can be safely treated as outpatients (38–40). Accordingly, a scenario

**Table 1.** Variables and sources*

| Model parameters | Mean estimate (range) | Source |
|---|---|---|
| Costs in 2012 Canadian dollars | | |
| Filgrastim 300 μg dose | 174† | Ontario Drug Benefit Formulary (28) |
| Pegfilgrastim 6 mg dose | 2422† | Ontario Drug Benefit Formulary (28) |
| Hospitalization for febrile neutropenia per day | 1012 (845–1273) | Lathia et al. (29) |
| Health utility values | | |
| NHL, baseline | 0.74 (IPI scores 0–1) and 0.44 (IPI scores 2–3)<br>Mean (0.59) of both IPI groups used in model (0.44–0.74) | Doorduijn et al. (30) |
| Hospitalization for febrile neutropenia | 0.15 less than value for NHL baseline (0.05–0.25 less than baseline value) | Lathia et al. (31) |
| Outpatient treatment for febrile neutropenia | 0.1 less than value for NHL baseline (used in scenario analysis) | Assumed |
| No febrile neutropenia | Parameters same as baseline NHL values | Not applicable |
| Febrile neutropenia | | |
| Probability of developing febrile neutropenia with no primary prophylaxis | 0.64 (0.57–0.71) | Meta-analysis (see Supplementary Appendix, available online) |
| Probability of developing febrile neutropenia with filgrastim | 0.36 (0.29–0.44) | Meta-analysis (see Supplementary Appendix, available online) |
| Probability of developing febrile neutropenia with pegfilgrastim | 0.21 (0.10–0.31) | Vose et al. (32) |
| Length of stay in hospital for febrile neutropenia | 8.2 days (6.2–10.2) | Caggiano et al. (33) |
| Duration of filgrastim therapy | 10 days (7–14) | Assumed based on current clinical practice at Sunnybrook Health Sciences Centre |
| Day on which febrile neutropenia occurs | Day 7 postchemotherapy | Cullen et al. (34) |

* IPI = International Prognostic Index; NHL = non-Hodgkin lymphoma.

† Medications costs assumed to be fixed, so no sensitivity analyses done.

International Prognostic Index

analysis was done where we assumed that 50% of febrile neutropenia patients were at low risk for complications and, as such, eligible for outpatient treatment after an initial in-hospital observation period. We assumed the cost of a 24-hour in-hospital observation period to be equal to the cost of hospitalization for 1 day.

### Quality of Life

Hospitalization for febrile neutropenia has been shown to adversely affect patients' quality of life and has been incorporated in the model as a decrement in the baseline health utility values of lymphoma patients. Utility values were collected from 26 patients with different types of underlying malignancies who were hospitalized for febrile neutropenia (31). We assumed that patients experience the utility decrement on the first day they develop febrile neutropenia and return to the baseline value after the febrile neutropenia episode resolves (ie, after hospital discharge).

### Costs

The costs of filgrastim, pegfilgrastim,and hospitalization for febrile neutropenia were included in the analysis. All costs were updated to 2012 Canadian dollars using the Bank of Canada Inflation Calculator (41). Costs of G-CSFs were obtained form the Ontario Drug Benefit Formulary, a publicly funded insurance program. The cost of hospitalization for febrile neutropenia was obtained from a Canadian study (29).

### Cost-Effectiveness Calculations and Sensitivity Analyses

We generated ICERs for filgrastim vs no primary prophylaxis (secondary prophylaxis), pegfilgrastim vs filgrastim primary prophylaxis, and pegfilgrastim vs no primary prophylaxis.

Sensitivity analyses were done to test the robustness of the results. One-way sensitivity analyses were done on all parameters, and changes in results were observed over the range of values tested. Ranges used are listed in Table 1. All ranges used were the 95% confidence intervals (CIs) of the parameters to assess variability on the population level. The 95% confidence intervals were not used for three parameters: the baseline utility value and length of stay because the 95% confidence intervals were too narrow to conduct meaningful analyses and the duration of filgrastim therapy because it was assumed, so the range was estimated from the medical literature. We conducted two one-way sensitivity analyses to test parameter values outside the plausible ranges for this analysis, but that may be applicable in other settings. One analysis tested a utility value for febrile neutropenia hospitalization of 0.36; this value was obtained from a surrogate population of nurses who cared for patients with febrile neutropenia and was used in previous cost-effectiveness analyses of G-CSFs (22,42,43). The other analysis used a daily hospitalization cost of CaD $3 000, which was assumed to account for higher US hospitalization costs. We conducted two additional one-way sensitivity analyses to test model assumptions. One analysis tested a 2.41-day shorter duration of

febrile neutropenia in patients who received filgrastim or pegfilgrastim prophylaxis, based on a meta-analysis that combined data from 148 clinical trials of G-CSFs done in patients with various types of malignancies (26), even though such a difference has not been demonstrated in lymphoma patients (19). The second analysis tested a 20% increase and decrease in the probability of febrile neutropenia with cycles two to six of chemotherapy because there are conflicting data on whether the risk of febrile neutropenia increases or decreases after the first cycle of chemotherapy (44).

A 3000-iteration probabilistic sensitivity analysis was done for each of the three ICERs generated to simultaneously reflect parameter uncertainty. Three distribution types were used in the probabilistic sensitivity analysis: beta distributions for probabilities of developing febrile neutropenia and health utilities; gamma distributions for costs and length of stay in hospital; and a uniform distribution for duration of filgrastim therapy because no information was available on the shape of this distribution. Cost-effectiveness acceptability curves were generated to examine the robustness of the results under various willingness-to-pay thresholds.

### Threshold analysis

We conducted a threshold analysis where the costs of filgrastim and pegfilgrastim were varied downward until the costs of these two strategies were equal to the mean cost of the no prophylaxis (secondary prophylaxis) strategy in the base-case analysis.

## Results

### Meta-analysis

The odds ratio for developing febrile neutropenia when receiving primary prophylaxis with filgrastim compared with no primary prophylaxis was 0.56 (95% CI = 0.41 to 0.77). Full details are found in the Supplementary Materials (available online).

### Base-Case Analysis

The total and incremental health outcomes and costs associated with all three strategies are detailed in Table 2. Costs associated with no primary prophylaxis, primary prophylaxis with 10 days of filgrastim, and primary prophylaxis with pegfilgrastim were CaD $7314, CaD $13947, and CaD $16290, respectively. The QALYs associated with the three strategies were 0.2004, 0.2015, and 0.2024, respectively. The ICER for filgrastim compared with no primary prophylaxis was CaD $5796000 per QALY; for pegfilgrastim compared with filgrastim primary prophylaxis, it was CaD $2611000 per QALY; and for pegfilgrastim compared with no primary prophylaxis, it was CaD $4396000 per QALY.

### Scenario Analyses

When we assumed that 50% of febrile neutropenia episodes would be eligible for outpatient treatment, the analysis yielded the following ICERs: CaD $8943000 per QALY for filgrastim vs no primary prophylaxis, CaD $6059000 per QALY for pefilgrastim vs filgrastim primary prophylaxis, and CaD $7788000 per QALY for pegfilgrastim vs no primary prophylaxis.

### One-Way Sensitivity Analyses

All one-way sensitivity analyses yielded ICERs greater than CaD $1000000 per QALY, except for the analysis that compared the filgrastim vs pegfilgrastim strategy when a daily hospitalization cost of CaD $3000 was used; this analysis yielded an ICER of CaD $466000 per QALY.

### Probabilistic Sensitivity Analysis

Iterations from the three probabilistic sensitivity analyses (Figure 1) indicate that primary prophylaxis with either filgrastim or pegfilgrastim is always associated with increased incremental costs for the filgrastim vs no primary prophylaxis and pegfilgrastim vs no primary prophylaxis strategies. The vast majority of iterations from the pegfilgrastim vs filgrastim strategy were also associated with increased incremental costs, with less than 1% of iterations associated with cost savings. Of iterations from the filgrastim vs no primary prophylaxis (secondary prophylaxis) strategy, the pegfilgrastim vs filgrastim primary prophylaxis strategy, and the pegfilgrastim vs no primary prophylaxis strategy, 62.5%, 60.1%, and 72.6%, respectively, were associated with health gains. Based on the cost-effectiveness acceptability curves (Figure 2), 20.0% of iterations would be cost-effective at a willingness-to-pay threshold of CaD $1595000 for the filgrastim vs no primary prophylaxis strategy (secondary prophylaxis), CaD $561000 for the pegfilgrastim vs filgrastim primary prophylaxis strategy, and CaD $2240000 for the pegfilgrastim vs no primary prophylaxis strategy.

### Threshold Analysis

If the cost of filgrastim were reduced to CaD $70 per dose (60% reduction), the cost of the 10-day filgrastim strategy would be equal

**Table 2.** Cost-effectiveness analysis results*

| Strategy | Cost, CaD $, 2012 (95% CI) | Effectiveness, QALDs (95% CI) | Effectiveness, QALYs (95% CI) | Incremental cost, CaD $ (95% CI) | Incremental effectiveness, QALYs (95% CI) | ICER, CaD $/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No primary prophylaxis | 7314 (6532 to 8104) | 73.14 (71.19 to 75.05) | 0.2004 (0.1950 to 0.2056) | ___† | ___† | ___† |
| Filgrastim | 13947 (12067 to 15748) | 73.56 (71.64 to 75.52) | 0.2015 (0.1963 to 0.2069) | 6633 (4602 to 8603) | 0.0011 (−0.0003 to 0.0024) | 5796000 (758000 to dominated) |
| Pegfilgrastim | 16290 (15821 to 16812) | 73.89 (71.97 to 75.69) | 0.2024 (0.1972 to 0.2074) | 2343 (469 to 4257) | 0.0009 (−0.0141 to 0.0161) | 2611000 (172000 to dominated) |

* CI = confidence interval; ICER = incremental cost-effectiveness ratio; QALD = quality-adjusted life day; QALY = quality-adjusted life years.

† Comparator strategy, no incremental data.

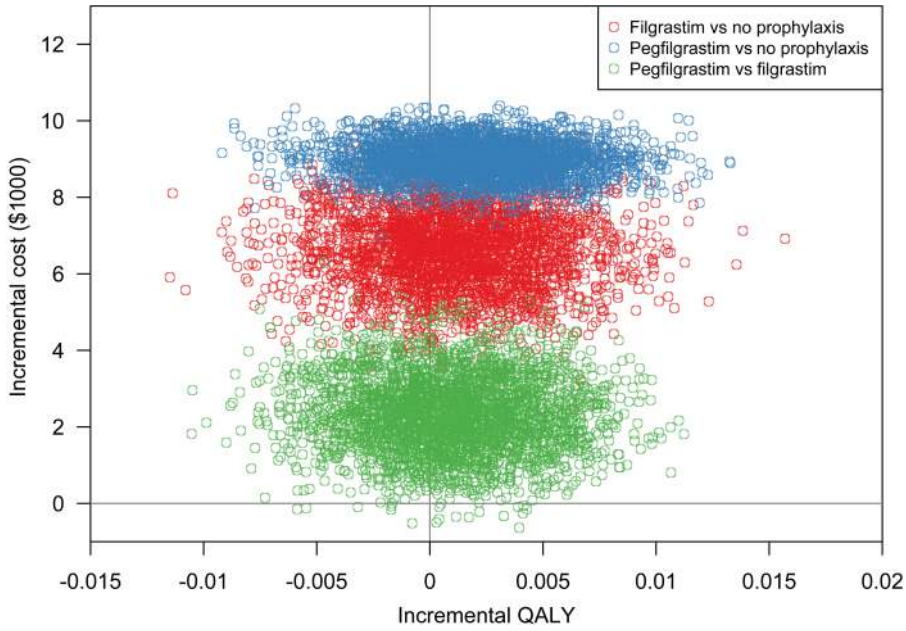


**Figure 1.** Results of probabilistic sensitivity analyses showing three groups of scatter plots on the cost-effectiveness plane: incremental costs and quality-adjusted life-years (QALYs) of filgrastim vs no primary prophylaxis, pegfilgrastim vs no primary prophylaxis, and pegfilgrastim vs filgrastim.

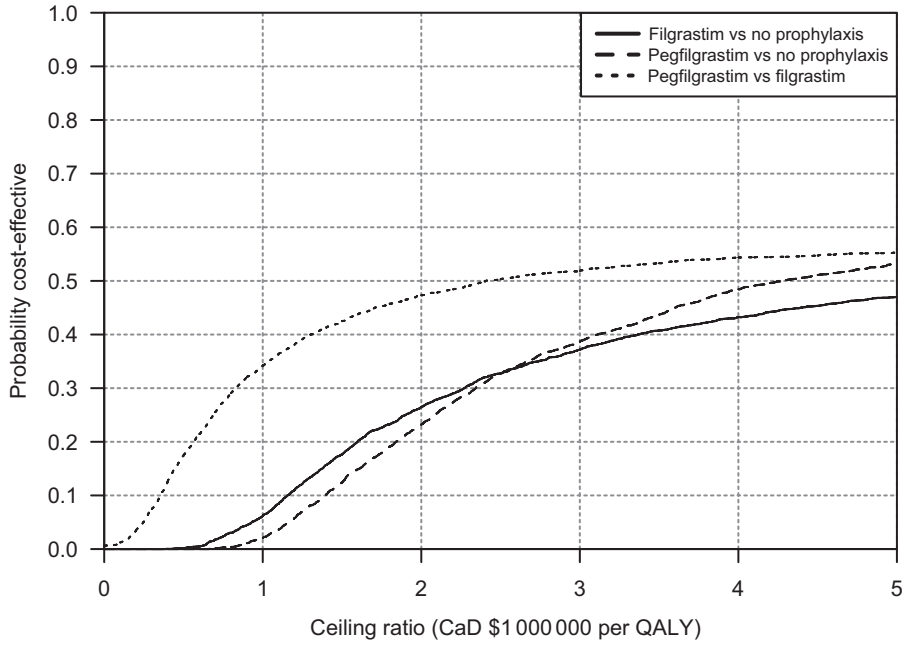


**Figure 2.** Cost-effectiveness acceptability curves for the incremental cost-effectiveness ratios (ICERs) of the three strategies evaluated: filgrastim vs no primary prophylaxis, pegfilgrastim vs no primary prophylaxis, and pegfilgrastim vs filgrastim. The x-axis represents various ICER ceiling ratios. The y-axis represents the probability of cost-effectiveness at the given ICER ceiling ratios. QALY = quality-adjusted life year.

to the cost of the no primary prophylaxis (secondary prophylaxis) strategy. If the cost of pegfilgrastim were reduced to CaD $908 (63% reduction), the cost of the pegfilgrastim strategy would be equal to the cost of the no primary prophylaxis (secondary prophylaxis) strategy.

## Discussion

The ICER for filgrastim compared with no prophylaxis (secondary prophylaxis) was CaD $5 796 000 per QALY when used as primary prophylaxis against febrile neutropenia in lymphoma patients. The ICER for pegfilgrastim compared with filgrastim was CaD $2 611 000 per QALY. Although there is no exact threshold for cost-effectiveness, tentative guidelines suggest CaD $20 000 to CaD $100 000 per QALY as a common reference point (45). The ICERs estimated in the current analysis are far above this range and well above the highest proposed value of CaD $200 000 per QALY (46,47), suggesting that neither of these interventions is cost-effective. The probabilistic sensitivity analyses indicate that our results are robust with respect to costs because almost all iterations were associated with increased

incremental costs, whereas only between 60% and 73% were associated with increased incremental QALYs.

Our findings are explained by the high costs of G-CSFs and the small health gains associated with their use. The primary benefit of G-CSFs is their effectiveness in preventing chemotherapy-induced febrile neutropenia (10,26,35). Although hospitalization for febrile neutropenia is costly, the cost of universal G-CSF primary prophylaxis outweighs that of febrile neutropenia treatment for patients who do develop this toxicity. G-CSFs do not improve overall survival or progression-free survival, as demonstrated by individual randomized trials in lymphoma patients (19–21) and meta-analyses (25–27), leading to very small QALY gains.

Recently published literature on G-CSFs includes cost-effectiveness analyses and discussions of G-CSF usage and its costs. All of the cost-effectiveness analyses of pegfilgrastim assumed a mortality benefit associated with its use, even though such a benefit has not been demonstrated in clinical trials. The ICERs resulting from these analyses range from pegfilgrastim being dominant (more effective and less costly) to CaD $US116 000 per QALY (12–18). One of these analyses was done in lymphoma patients and yielded ICERs of CaD $6 190 per QALY when a febrile neutropenia-related mortality benefit was assumed, and CaD $1 677 per QALY when a long-term mortality benefit was assumed (14). The much lower ICERs from these analyses, compared with ours, clearly resulted from the inclusion of a mortality benefit. The one paper that examined the cost-effectiveness of filgrastim did not assume a mortality benefit with its use; however, the authors included a death state in the model and varied its relative risk in their sensitivity analysis despite a model time horizon of only eight chemotherapy cycles (22). Overall survival from randomized trials was evaluated over a much longer time period (1.3 to 7.9 years) (25), providing more relevant data on long-term mortality. This analysis yielded an ICER of CaD $700 000 per QALY. The lower ICER estimate compared with ours is related to the lower febrile neutropenia health utility value used, the disutility assumed with delayed chemotherapy, and the longer in-hospital stay assumed for febrile neutropenia treatment. Despite the different underlying assumptions and resulting ICER estimate compared with our analysis, the conclusion that filgrastim is not cost-effective is robust because both ICERs are well above any acceptable cost-effectiveness threshold.

Two publications have examined G-CSF use and its costs. One study reported that 96% of G-CSF use in lung and colorectal cancer patients was not supported by evidence-based guidelines (48). The authors suggest that decreasing inappropriate use of G-CSFs would yield considerable cost savings. The second publication, a commentary on decreasing cancer costs in the United States, noted that G-CSF provides fewer clinical benefits than anticipated, most notably no mortality benefit (49). With current G-CSF sales at over CaD $5.2 billion annually (50), decreasing use of these agents, where appropriate, would reduce costs without affecting patient outcomes.

There were two main limitations to our study. First, some data we used were taken from studies conducted in patient populations other than the one considered in this analysis. Specifically, data on costs of treating febrile neutropenia in hospital and health utility values associated with hospitalization for febrile neutropenia were collected in patients with a variety of underlying malignancies. Also, the probability of developing febrile neutropenia with pegfilgrastim was based on one study that considered lymphoma patients who were experiencing a disease relapse and receiving chemotherapy other than R-CHOP. Second, this analysis was conducted from the perspective of a publicly funded health-care system and did not account for broader societal or indirect costs, such as lost productivity or caregiver burden.

Future work should evaluate the cost-effectiveness of alternate strategies for preventing febrile neutropenia, including reducing the cost of G-CSF (48). Results of this work will inform clinicians and health-care decision makers about the relative efficiency of these interventions compared with current G-CSF use.

Our results indicate that neither filgrastim nor pegfilgrastim are cost-effective as primary prophylaxis against febrile neutropenia in lymphoma patients. They provide further evidence against routine use of these interventions and bolster recent arguments (47,48) that reducing G-CSF use would result in considerable cost savings without adversely affecting patient outcomes.

## References


1. National Cancer Institute. *SEER Cancer Statistics Review 1975–2008*. http://seer.cancer.gov/statistics/. Accessed August 26, 2011.
2. National Cancer Institute. *A Snapshot of Lymphoma*. http://www.cancer.gov/aboutnci/servingpeople/snapshots/lymphoma.pdf. Accessed August 26, 2011.
3. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. *Blood*. 2006;107(1):265–276.
4. Freedman AS, Freidberg, JW. Initial treatment of advanced stage diffuse large B cell lymphoma. www.uptodate.com. Accessed July 23, 2012.
5. Pettengell R, Linch D, Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Position paper on the therapeutic use of rituximab in CD20-positive diffuse large B-cell non-hodgkin's lymphoma. *Br J Haematol*. 2003;121(1):44–48.
6. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol*. 2005;23(22):5027–5033.
7. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):e56–e93.
8. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera international trial (MInT) group. *Lancet Oncol*. 2006;7(5):379–391.
9. Pfreundschuh M, Schubert J, Ziepert M, et al. German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol*. 2008;9(2):105–116.
10. 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(21):3158–3167.
11. Smith TJ, 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(19):3187–3205.
12. Borget I, Di Palma M, Leonard R. Pegfilgrastim—a health economic model to assess overall cost-effectiveness. *Eur J Hospital Pharm Prac*. 2009;15:58–61.
13. Eldar-Lissai A, Cosler LE, Culakova E, Lyman GH. Economic analysis of prophylactic pegfilgrastim in adult cancer patients receiving chemotherapy. *Value Health*. 2008;11(2):172–179.

14. Lyman G, Lalla A, Barron R, Dubois RW. Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. *Curr Med Res Opin*. 2009;25(2):401–411.
15. Lyman GH, Lalla A, Barron RL, Dubois RW. Cost-effectiveness of pegfilgrastim versus filgrastim primary prophylaxis in women with early-stage breast cancer receiving chemotherapy in the United States. *Clin Ther*. 2009;31(5):1092–1104.
16. Liu Z, Doan QV, Malin J, Leonard R. The economic value of primary prophylaxis using pegfilgrastim compared with filgrastim in patients with breast cancer in the UK. *Appl Health Econ Health Policy*. 2009;7(3):193–205.
17. Ramsey SD, Liu Z, Boer R, et al. Cost-effectiveness of primary versus secondary prophylaxis with pegfilgrastim in women with early-stage breast cancer receiving chemotherapy. *Value Health*. 2009;12(2):217–225.
18. Danova M, Chiroli S, Rosti G, Doan QV. Cost-effectiveness of pegfilgrastim versus six days of filgrastim for preventing febrile neutropenia in breast cancer patients. *Tumori*. 2009;95(2):219–226.
19. Doorduijn JK, van der Holt B, van Imhoff GW, et al. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2003;21(16):3041–3050.
20. Zinzani PL, Pavone E, Storti S, et al. Randomized trial with or without granulocyte colony-stimulating factor as adjunct to induction VNCOP-B treatment of elderly high-grade non-Hodgkin's lymphoma. *Blood*. 1997;89(11):3974–3979.
21. Pettengell R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood*. 1992;80(6):1430–1436.
22. Chan KKW, Siu E, Krahn MD, Imrie K, Alibhai SMH. Cost-utility analysis of primary prophylaxis versus secondary prophylaxis with granulocyte colony-stimulating factor in elderly patients with diffuse aggressive lymphoma receiving curative-intent chemotherapy. *J Clin Oncol*. 2012;30(10):1064–1071.
23. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics*. 2006;24(4):355–371.
24. Freedman AS, Aster JC. Epidemiology, clinical manifestations, pathologic features, and diagnosis of diffuse large B cell lymphoma. www.uptodate.com. Accessed August 3, 2011.
25. Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. *Cochrane Database Syst Rev*. 2008;4:CD003189.
26. Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J. Meta-analysis: Effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. *Ann Intern Med*. 2007;147(6):400–411.
27. Lyman GH, Dale DC, Wolff DA, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. *J Clin Oncol*. 2010;28(17):2914–2924.
28. Ontario Ministry of Health and Long-Term Care. *Ontario Public Drug Programs Formulary*. http://www.health.gov.on.ca/english/providers/program/drugs/odbf_mn.html. Accessed March 2, 2013.
29. Lathia N, Mittmann N, DeAngelis C, et al. Evaluation of direct medical costs of hospitalization for febrile neutropenia. *Cancer*. 2010;116(3):742–748.
30. Doorduijn J, Buijt I, Holt B, Steijaert M, Uyl-de Groot C, Sonneveld P. Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy. *Eur J Haematol*. 2005;75(2):116–123.
31. Lathia N. *Evaluation of Direct Medical Cost, Lost Productivity, Health Utility and Quality of Life in Patients Hospitalized for Febrile Neutropenia [dissertation]*. Toronto, Ontario, Canada: University of Toronto; 2008.
32. Vose JM, Crump M, Lazarus H, et al. Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. *J Clin Oncol*. 2003;21(3):514–519.
33. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer*. 2005;103(9):1916–1924.
34. Cullen M. Steven N. Billingham L. et al. Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotic in a Number of Tumours (SIGNIFICANT) Trial Group. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med*. 2005;353(10):988–998.
35. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. *Am J Med*. 2002;112(5):406–411.
36. Timmer-Bonte JN, Adang EM, Smit HJ, et al. Cost-effectiveness of adding granulocyte colony-stimulating factor to primary prophylaxis with antibiotics in small-cell lung cancer. *J Clin Oncol*. 2006;24(19):2991–2997.
37. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. 2006;24(19):3121–3127.
38. Cherif H, Johansson E, Bjorkholm M, Kalin M. The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. *Haematologica*. 2006;91(2):215–222.
39. Innes H, Lim SL, Hall A, Chan SY, Bhalla N, Marshall E. Management of febrile neutropenia in solid tumours and lymphomas using the multinational association for supportive care in cancer (MASCC) risk index: feasibility and safety in routine clinical practice. *Support Care Cancer*. 2008;16(5):485–491.
40. 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(25):4129–4134.
41. Bank of Canada. *Inflation Calculator*. http://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed March 2, 2013.
42. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. *Pharmacoeconomics*. 2001;19(11):1091–1102.
43. Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the united kingdom. *Value Health*. 2011;14(4):465–474.
44. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia risks, consequences, and new directions for its management. *Cancer*. 2004;100(2):228–237.
45. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ*. 1992;146(4):473–481.
46. Hillner BE, Smith TJ. Efficacy does not necessarily translate to cost effectiveness: a case study in the challenges associated with 21st-century cancer drug pricing. *J Clin Oncol*. 2009;27(13):2111–2113.
47. Braithwaite RS, Meltzer DO, King JT, Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care*. 2008;46(4):349–356.
48. Potosky AL, Malin JL, Kim B, et al. Use of colony-stimulating factors with chemotherapy: ppportunities for cost savings and improved outcomes. *J Natl Cancer Inst*. 2011;103(12):979–982.
49. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med*. 2011;364(21):2060–2065.
50. Amgen Inc. Amgen media news release. http://www.amgen.com/media/media_pr_detail.jsp?year=2012&releaseID=1653300. Accessed July 23, 2012.

## Funding

This work was supported by a Clinical Research Fellowship from the Canadian Institutes of Health Research (CFE-109446) that was awarded to NL and an unrestricted educational grant from Amgen Canada that was awarded to NM and NL.

## Notes

Neither the Canadian Institutes of Health Research nor Amgen Canada played any role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

**Affiliations of authors:** Department of Pharmaceutical Sciences (NL, CDA, JSH, SW), Department of Pharmacology (NM), and Department of Health Policy, Management and Evaluation (JSH), University of Toronto, Toronto, Ontario, Canada; Department of Pharmacy (NL, CDA, SW), Health Outcomes and PharmacoEconomics (HOPE) Research Centre, Division of Clinical Pharmacology, Sunnybrook Research Institute (PKI, NM), and Department of Medicine, Division of Hematology/Oncology (MC), Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, Maryland (TJS); International Centre for Health Innovation, Richard Ivey School of Business, University of Western Ontario, London, Ontario, Canada (NM); Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada (JSH); Pharmacoeconomics Research Unit, Cancer Care Ontario, Toronto, Ontario, Canada (JSH).