Cost of neutropenic complications of chemotherapy

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Received 25 January 2007; revised 28 August 2007; accepted 11 October 2007

Background: Cost of neutropenic complications of myelosuppressive chemotherapy has been reported to be substantial. Prior research, however, has focused on initial hospitalization only and has failed to account for follow-on care.

Patients and methods: Using a US health-care claims database, all adult cancer patients who received a course of chemotherapy were identified. For each such patient, each unique cycle of chemotherapy within the course and each occurrence of neutropenic complications within these cycles were characterized. Patients developing neutropenic complications in a given cycle (neutropenia patients), starting with the first, were matched (1 : 1) to those who did not develop neutropenic complications in that cycle (comparison patients), and health-care costs (i.e. expenditures) were tallied for each matched pair.

Results: Neutropenia patients (n = 373) and comparison patients were similar in terms of baseline characteristics. Costs of neutropenia-related care were $12,397 (95% confidence interval $10,274–$14,754) higher for neutropenia versus comparison patients [$14,407 ($12,357–$16,743) versus $2010 ($1490–$2553)]. Among neutropenia patients, mean cost of initial hospitalization for neutropenic complications was $7813 ($6537–$9379); cost of all subsequent neutropenia-related care averaged $6594 ($5217–$8272).

Conclusions: Neutropenic complications of myelosuppressive chemotherapy are costly. Prior research focusing on initial hospitalization only may have underestimated the cost of these complications by as much as 40%.

Key words: costs and cost analysis, fever, infection, neoplasms, neutropenia

Introduction

Neutropenia is a common complication of myelosuppressive chemotherapy that increases the risk of serious, often life-threatening, infections [1]. Although fever is often the first sign of serious infection in neutropenic patients, less than one-half of patients presenting with febrile neutropenia are ultimately found to have a clinically identified (i.e. documented) infection [2, 3]. Hospital admission for administration of i.v. antibiotics is the standard of care for both febrile neutropenia and infections associated with neutropenia [4].

The cost of hospitalization for chemotherapy-related neutropenic complications is substantial [5–7]. In two recent comprehensive studies, the mean cost of these hospitalizations was reported to be $13,372 and $19,110 [6, 7]. The true cost of neutropenic complications in patients receiving myelosuppressive chemotherapy may be even higher than these estimates (and others published to date), however, as they were determined on the basis of the resource use during the initial hospitalization only. Potentially important follow-on care related to the initial event—including postdischarge outpatient care, laboratory tests, antibiotics, and filgrastim therapy—was not considered. Moreover, patients who develop neutropenic complications during a given cycle of chemotherapy may be at elevated risk of subsequent episodes of febrile neutropenia or infection requiring inpatient and/or outpatient care. As these potential downstream consequences have not been considered in research to date, we undertook a study to estimate the total cost of neutropenic complications in patients receiving myelosuppressive chemotherapy.

Patients and methods

Overview

A retrospective cohort study was undertaken using a large US health-care claims database. Study subjects consisted of cancer patients, aged ≥18 years, who received a course of chemotherapy. For each such patient, each unique cycle of chemotherapy within the course was characterized, and occurrences of neutropenic complications in these cycles were identified on the basis of hospitalization for neutropenia, fever, and/or infection. Patients who were hospitalized for neutropenic complications in a given cycle (neutropenia patients), starting with the first, were matched to patients who were not hospitalized for neutropenic complications in that cycle (comparison patients), regardless of the occurrence of such complications in subsequent cycles. Health-care costs—overall and for neutropenia-related care—were tallied for each matched pair, beginning with the cycle...
day on which the neutropenic complication was first noted (for the neutropenia patient) through the end of the last cycle of chemotherapy within the course.

**data source**
Data were obtained from a large US health-care claims database (Ingenix LabRx, Ingenix Health Intelligence, Salt Lake City, UT) and spanned the period 1 January 2001 through 31 December 2003. The database comprises information from facility (e.g. hospital), professional service (e.g. physician), and retail pharmacy (i.e. outpatient medication) claims that were submitted for reimbursement to a single United States health insurer. Types of coverage available from the insurer include commercial health maintenance organization, preferred provider organization, and other managed care and indemnity products. Members include an employed population and their dependents (10 million covered lives annually) residing across a wide geographic area in the United States. Approximately 4% of persons in the database are aged 65 years.

Data available for each facility and professional service claim include date and place of service, diagnoses, procedures (in International Classification of Diseases, ninth edition, Clinical Modification (ICD-9-CM) format), procedures carried out/services rendered (in ICD-9-CM or Health-Care Financing Administration Common Procedure Coding System (HCPCS) format), and quantity of services rendered (professional service claims only). Data available for each retail pharmacy claim include the drug dispensed (in National Drug Code (NDC) format), dispensing date, quantity dispensed, and number of therapy-days supplied. Each claim includes the amount charged by the health-care provider and the amount paid by the health-care organization. Selected demographic and eligibility information also is available for all persons, including age, sex, geographic region, coverage type, and the start and end dates of health-care coverage.

All patient identifiers in the database have been encrypted, and the database is fully compliant with the Health Insurance Portability and Accountability Act of 1996 [8]. Since “…subjects cannot be identified, directly or through identifiers linked to the subjects …” (45 CFR 46 §46.101), institutional review board approval for this study was neither needed nor sought [9].

**source population**
All patients aged 218 years were identified who had one or more medical claims with a HCPCS code for a chemotherapy drug or administration of chemotherapy from 1 July 2001 to 31 March 2003. Among these patients, attention was limited to those who began a course of chemotherapy during this period; initiation of a course of chemotherapy was defined on the basis of the date of the first claim for a chemotherapy drug or administration of chemotherapy that was preceded by a 180-day period without any such claims. Among patients beginning a course of chemotherapy, attention was further limited to those who had two or more medical claims (≥27 days apart) with a diagnosis code for a primary cancer of the same body site during the 180-day period preceding (and including) the date of initiation of chemotherapy.

Patients were excluded from the source population if they: (i) had a claims history indicating the presence of primary cancers in two different body sites; (ii) had any claims for hematopoietic stem cell transplantation; or (iii) were not continuously eligible for comprehensive health-care coverage during the 180-day period preceding the date of initiation of chemotherapy.

**chemotherapy cycles**
For each patient in the source population, each unique cycle of chemotherapy within the course was characterized. The first cycle was defined as beginning on the date of initiation of chemotherapy and ending with the first service date for the next administration of chemotherapy. (Chemotherapy agents administered within 6 days of cycle start were considered part of the first cycle’s regimen.) If a second cycle of chemotherapy did not begin before day 60 or if radiation therapy was initiated during this period, then the first cycle of chemotherapy (and the chemotherapy course) was considered complete 60 days following the date of initiation of chemotherapy or on the date radiation treatment began, whichever occurred first. The second and all subsequent cycles of chemotherapy were similarly defined, up to a maximum of nine cycles in total. Because the duration of intervals between chemotherapy administrations is dependent, in part, on recovery time from associated toxic effects, and because chemotherapy drugs that cause myelosuppression are typically administered every 3–4 weeks, only patients whose cycles were all at least 20 days (but not >59 days) in duration were considered for analysis.

**chemotherapy regimen**
All cycles of chemotherapy were stratified according to the regimen on the basis of a review of drug codes on all medical claims with service dates within 6 days of the start of the chemotherapy cycle. Regimens were categorized as highly myelosuppressive or not on the basis of the drugs administered (list of drugs is available in on-line supplement). Patients for whom one or more cycle-specific regimens could not be determined were dropped from the source population.

**neutropenic complications**
For each patient in the source population, all chemotherapy cycles in which neutropenic complications occurred (if any) were identified. Neutropenic complications were identified on the basis of hospitalizations with a primary or secondary diagnosis of neutropenia (ICD-9-CM 288.0), fever (780.6), or infection (list available from authors upon request). Patients with such hospitalizations in more than one cycle were classified according to the cycle number in which the first hospitalization occurred.

**sequential matching**
Patients who were hospitalized for neutropenic complications during their first cycle of chemotherapy (neutropenia patients) were matched on selected characteristics to patients who were not hospitalized for neutropenic complications in their first cycle of chemotherapy (comparison patients), whether or not they developed such complications in subsequent cycles. Neutropenia patients and comparison patients matched during the first cycle were then removed from the source population. From patients remaining in the source population, those who were first hospitalized for neutropenic complications in the second cycle of chemotherapy were then matched to those who did not have such a hospitalization in that cycle; both of these groups were then removed from the source population before next cycle matching. Neutropenia patients and comparison patients in the third and all subsequent cycles were similarly matched. (A matching procedure was employed to minimize the potential for confounding due to differences between neutropenia patients and comparison patients in characteristics that were hypothesized to be associated with neutropenic complications and health-care costs.)

Neutropenia patients and comparison patients were matched (1:1:1) in each cycle on the basis of tumor type, total number of cycles during the course of chemotherapy, and chemotherapy regimen (highly myelosuppressive: yes/no). In addition, because the two groups may have differed with respect to many other characteristics possibly associated with neutropenic complications and health-care costs, and
because matching on all such characteristics individually was deemed infeasible, we further matched cohorts on the basis of their estimated propensity scores [i.e. the predicted probability of being a neutropenia patient (versus a comparison patient)], within 0.1 (on a scale of 0–1) [10, 11]. The propensity score was estimated using logistic regression; independent variables included age, sex, geographic region of residence, type of insurance coverage, selected comorbidities, an adapted version of the Charlson comorbidity index, history of anemia, hospitalization, radiation therapy, antibiotic therapy and granulocyte colony-stimulating factor (G-CSF) therapy, total (precycle) health-care costs, tumor type, presence of metastases, chemotherapy regimen, and cycle number [12]. Age, geographic region of residence, and type of insurance coverage were assessed as of the first day of the corresponding cycle of chemotherapy. All other characteristics were assessed beginning 180 days before the initiation of chemotherapy and ending on the fifth day of the corresponding cycle or the day before the onset of neutropenic complications, whichever occurred first. Presence of metastases was identified on the basis of corresponding ICD-9-CM diagnoses codes. Receipt of G-CSF was ascertained on the basis of medical claims with HCPCS codes for filgrastim (J1440, J1441), pegfilgrastim (C9119, S0135), and pharmacy claims with corresponding NDC codes.

**health-care costs**

Health-care costs were tallied for each neutropenia patient and matched comparison patient from the date of onset of neutropenic complication (for the former) through the end of the last cycle of chemotherapy. Costs were examined on an overall basis (i.e. for all care) and for neutropenia-related care only. Neutropenia-related care included all inpatient and outpatient encounters—with an ICD-9-CM diagnosis code—for neutropenia, infection, or fever, as well as all G-CSF and antibiotic therapy. Costs were estimated on the basis of reimbursed amounts (i.e. third-party payer expenditures).

For all neutropenia patients, neutropenia-related costs were stratified into those for initial hospitalization, postdischarge care through end of cycle, and neutropenia-related care in all subsequent cycles. For comparison patients, neutropenia-related costs were stratified into those for the index and those for all subsequent cycles. (While comparison patients, by definition, could not have been hospitalized for neutropenic complications in the index cycle, they may have received outpatient care for neutropenia, fever, or infection during this period and thus have neutropenia-related costs in the index cycle.) Neutropenia-related costs incurred after the index cycle were further categorized for neutropenia patients and comparison patients into those for G-CSF prophylaxis—defined as receipt on or before cycle day 5—and all other neutropenia-related care [13].

**statistical analyses**

Demographic and clinical characteristics of neutropenia patients and comparison patients were examined to assess the adequacy of the matching procedure. Categorical variables were compared using the McNemar or Bowker test, and a paired samples t-test or Wilcoxon signed rank test was used for continuous measures, as appropriate. Health-care utilization was examined descriptively for neutropenia patients and comparison patients from the date of hospital admission for neutropenic complications (for the former) through the last chemotherapy cycle. Total and neutropenia-related health-care costs for neutropenia patients and comparison patients, and corresponding differences between groups, were summarized using means and 95% confidence intervals (CIs); 95% CIs were generated using techniques of nonparametric bootstrapping. The cost of neutropenic complications also was summarized using a more conservative approach, including only the cost of initial hospitalization, neutropenia-related costs among neutropenia patients during the remainder of the cycle in which the initial hospitalization occurred, and the difference in costs of G-CSF prophylaxis between neutropenia patients and comparison patients beyond the index cycle (i.e. excluding costs of subsequent neutropenic complications).

**results**

**patient characteristics**

A total of 15,420 patients aged ≥18 years began a new course of chemotherapy for a specified primary cancer during the period of interest. Fifty-eight percent (n = 8,979) of these patients had only cycles of 20 days or more and, of these patients, 50% (n = 4,471) had available for each cycle information on their chemotherapy regimen and thus were included in the source population. Mean age [standard deviation (SD)] of patients in the source population was 52 (10) years and 73% were women. Breast cancer was the most common malignancy (52%), followed by lung cancer (14%), geriatric cancer (10%), and non-Hodgkin’s lymphoma (NHL) (8%).

Among all patients in the source population, 197 (4%) were hospitalized for complications of neutropenia during their first cycle of chemotherapy; in all remaining cycles, an additional 176 neutropenia patients were identified and matched to comparison patients. Two-thirds of the 373 neutropenia patients were hospitalized for complications of neutropenia during their first or second cycle of chemotherapy. Twenty-four percent of all neutropenia patients received only one cycle of chemotherapy (46% among those developing neutropenic complications during cycle one). Neutropenia patients and comparison patients were (by design) similar in terms of baseline characteristics (Table 1). Forty-four percent of the study population resided in the southern United States, while 37% resided in the Midwestern United States. Over one-half were enrolled in a health maintenance organization, 18% in a preferred provider organization, and 18% in a point of service organization. Mean (±SD) duration of the chemotherapy course was 153 (±97) days for neutropenia patients versus 147 days (±85) for comparison patients; corresponding medians were 133 and 130 days.

**health-care utilization and costs**

Neutropenia patients averaged 1.2 (±0.5) neutropenia-related hospital admissions (including the initial hospitalization) versus 0.1 (±0.3) for comparison patients; corresponding figures for all-cause admissions were 1.4 (±0.7) and 0.2 (±0.5) (Table 2). Neutropenia patients also averaged 7.7 (±9.8) neutropenia-related outpatient encounters, while comparison patients averaged 2.3 (±5.8); the mean number of encounters for chemotherapy was 3.2 (±4.4) and 3.5 (±4.3), respectively.

Mean total health-care costs (per patient) were $13,167 (95% CI $9,624–$17,014) higher among neutropenia patients versus comparison patients ($30,839 [$27,917–$34,168] versus $17,672 [$15,902–$19,513]) (Table 3). This difference was due almost entirely to a difference of $12,397 ($10,274–$14,754) in costs of neutropenia-related care.
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia patients (n = 373)</th>
<th>Comparison patients (n = 373)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>54.5 ± 11.0</td>
<td>53.7 ± 10.7</td>
<td>0.375</td>
</tr>
<tr>
<td>Female, %</td>
<td>65.3</td>
<td>64.3</td>
<td>0.761</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>22.8</td>
<td>20.4</td>
<td>0.423</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>1.3</td>
<td>1.1</td>
<td>0.737</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>4.8</td>
<td>4.6</td>
<td>0.863</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>2.1</td>
<td>2.7</td>
<td>0.633</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0.8</td>
<td>1.3</td>
<td>0.477</td>
</tr>
<tr>
<td>Rheumatologic disease</td>
<td>2.7</td>
<td>1.9</td>
<td>0.462</td>
</tr>
<tr>
<td>None of the above</td>
<td>70.0</td>
<td>72.7</td>
<td>0.418</td>
</tr>
<tr>
<td>Clinical comorbidity, index, mean ± SD</td>
<td>5.9 ± 3.2</td>
<td>5.5 ± 3.2</td>
<td>0.073</td>
</tr>
<tr>
<td>History of anemiaa, %</td>
<td>30.3</td>
<td>29.5</td>
<td>0.810</td>
</tr>
<tr>
<td>History of hospitalizationb, %</td>
<td>63.0</td>
<td>58.4</td>
<td>0.202</td>
</tr>
<tr>
<td>History of radiation therapyb, %</td>
<td>14.7</td>
<td>14.5</td>
<td>0.917</td>
</tr>
<tr>
<td>History of antibiotic therapyb, %</td>
<td>69.4</td>
<td>64.9</td>
<td>0.185</td>
</tr>
<tr>
<td>History of G-CSF therapyb, %</td>
<td>11.8</td>
<td>15.0</td>
<td>0.197</td>
</tr>
<tr>
<td>Health-care costs before index cyclec, mean ± SD</td>
<td>27 412 ± 23 636</td>
<td>25 308 ± 21 582</td>
<td>0.172</td>
</tr>
</tbody>
</table>

### Table 2. Health-care utilization from the date of initial hospitalization for neutropenic complications (for neutropenia patients) through the end of chemotherapy course

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Neutropenia patients (n = 373)</td>
<td>Comparison patients (n = 373)</td>
</tr>
</tbody>
</table>

#### Inpatient care

- All hospitalizations, no.  
  - Admissions 1.4 ± 0.7  
  - Days 8.9 ± 0.9  
  - Neutropenia-related hospitalizationsa, no.  
    - Admissions 1.2 ± 0.5  
    - Days 8.0 ± 0.8  

#### Outpatient care

- All office, clinic, Emergency room encounters, no.  
  - Chemotherapy encounters 3.2 ± 4.4  
  - Neutropenia-related encountersb  
    - Other encounters 16.7 ± 16.0  

#### Outpatient medication

- All Rx’s dispensed, no. 12.4 ± 13.7  
- Antibiotic Rx’s dispensed, no. 1.3 ± 1.6

*Includes admissions with primary or secondary diagnosis of neutropenia, fever, or infection; some comparison patients were hospitalized for neutropenic complications after the index cycle.

bIncludes encounters with diagnosis of neutropenia, fever, and/or infection and encounters for granulocyte colony-stimulating factor or antibiotic therapy.

cDispensed by retail pharmacy.

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*Assessed from beginning of the 180-day prechemotherapy period to the fifth day of corresponding cycle.

SD, standard deviation; G-CSF, granulocyte colony-stimulating factor; CNS, central nervous system.
comparison patients were 29% and 71% (25% or $323). The alternative, more conservative estimate of the cost of neutropenic complications determined on the basis of initial hospitalization and same-cycle neutropenia-related care for neutropenia patients, and the difference in costs of G-CSF prophylaxis beyond the index cycle—was thus $11,041 ($7,813 + $2,485 + ($1,066–$323)).

**discussion**

Using a large US health-care claims database, we estimated the total cost of neutropenic complications of myelosuppressive chemotherapy, including initial hospitalization as well as all downstream neutropenia-related care. Our findings indicate that the cost of neutropenic complications may be substantially higher than previously estimated [5–7]. For example, in the study by Caggiano et al. [6], the cost of neutropenic hospitalizations for breast cancer, lung cancer, and NHL patients—who represent >70% of our study sample—was reported to range from $7,100 to $11,600. While these figures (despite differences in study design and study populations) are comparable to our own estimate of the cost of hospitalization for neutropenic complications ($7,813), we found that this cost represented only ~60% of the total economic burden of neutropenia-related care (i.e. $12,397, equal to the difference in costs between neutropenia patients and comparison patients) with the rest attributable to downstream, postdischarge costs. Clinical guidelines recommend the use of primary prophylaxis with CSFs when a patient’s risk of febrile neutropenia is ~20% (or greater) and indicate—on the basis of currently available evidence—that use of these agents may be justified on purely economic grounds (i.e. cost saving) when the rate of febrile neutropenia approaches 40% [14]. This figure (i.e., 40%), however, was determined on the basis of a cost estimate that includes only the initial hospitalization for febrile neutropenia [4]. Thus, to the extent that the costs of febrile neutropenia were underestimated in previous work, as indicated by the results of our study, the risk threshold at which the use of CSFs may be cost saving may be considerably lower and much closer to the new clinical threshold regarding the use of these agents (20% risk of febrile neutropenia). Our study thus underscores the importance of accurately estimating the full burden of disease when evaluating the cost-effectiveness of medical interventions. It should be noted that disease burden estimated in our study does not include any so-called indirect costs, such as work and productivity loss, nor do we consider the health benefits of CSFs (i.e., life years gained associated with the decreasing risk of febrile neutropenia and its attendant mortality). Ideally, future studies of the cost of neutropenic complications and

Table 3. Health-care costs from the date of initial hospitalization for neutropenic complications (for neutropenia patients) through the end of chemotherapy course

<table>
<thead>
<tr>
<th></th>
<th>Mean costs per patient (95% confidence interval)</th>
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<tbody>
<tr>
<td></td>
<td>Neutropenia patients</td>
</tr>
<tr>
<td></td>
<td>(n = 373)</td>
</tr>
<tr>
<td>All care</td>
<td>30.839 (27.917, 34.168)</td>
</tr>
<tr>
<td>Neutropenia-related care</td>
<td>14.407 (12.357, 16.743)</td>
</tr>
<tr>
<td>Non-neutropenia-related care</td>
<td>16.432 (14.676, 18.361)</td>
</tr>
<tr>
<td>Inpatient care</td>
<td></td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>10.823 (9.179, 12.800)</td>
</tr>
<tr>
<td>Neutropenia-related hospitalizations</td>
<td>9.881 (8.347, 11.851)</td>
</tr>
<tr>
<td>Outpatient care</td>
<td></td>
</tr>
<tr>
<td>All office, clinic, Emergency room encounters, no.</td>
<td>18.607 (16.547, 20.877)</td>
</tr>
<tr>
<td>Chemotherapy encounters</td>
<td>6.671 (5.698, 7.670)</td>
</tr>
<tr>
<td>Neutropenia-related encounters</td>
<td>4.457 (3.530, 5.578)</td>
</tr>
<tr>
<td>Other encounters</td>
<td>7.479 (6.584, 8.483)</td>
</tr>
<tr>
<td>Outpatient medication</td>
<td></td>
</tr>
<tr>
<td>All pharmacotherapy</td>
<td>1.409 (1.092, 1.797)</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td>0.69 (0.58, 0.82)</td>
</tr>
</tbody>
</table>

*Includes all neutropenia-related hospitalizations, neutropenia-related outpatient encounters, and outpatient G-CSF and antibiotic therapy.

*Includes admissions with diagnosis of neutropenia, fever, and/or infection.

*Includes encounters with diagnosis of neutropenia, fever, and/or infection and encounters for G-CSF or antibiotic therapy.

G-CSF, granulocyte colony-stimulating factor.

**Figure 1.** Cost of neutropenia-related care.
cost-effectiveness of CSFs (and other interventions) will take into account these additional components of disease burden.

Although neutropenia patients and comparison patients were matched on several characteristics, one limitation of our study is the possibility that the two cohorts differed in terms of unobserved characteristics that predispose to neutropenic complications. To the extent that neutropenia patients in our study were more likely to develop neutropenic complications than comparison patients, some downstream costs—in particular, those occurring in cycles after the one in which initial hospitalization occurred—should not be attributed to the neutropenic complications per se. Our alternative, more conservative estimate of the cost of neutropenic complications, however, was similar to our basecase estimate ($11,041 versus $12,397), indicating that the magnitude of any such bias is probably small.

Several generic limitations of retrospective studies employing health-care claims data also should be noted. All such databases, contain errors of omission and commission in coding. In addition, certain biases in coding may exist such that patients who are hospitalized for neutropenic complications may be more likely to have ‘neutropenia’ (ICD-9-CM 288.0) designated as a secondary (or even primary) diagnosis on future encounters versus patients without a history of these complications, all else equal. Moreover, information often is not available for one or more clinically important parameters (in our study, absolute neutrophil counts, patient tumor stage, bone marrow involvement, and performance status), and pertinent medical history can be left censored (e.g. receipt of chemotherapy and neutropenic complications occurring before the time period of the study database are unobservable). The impact of these limitations on our study cannot be assessed. We note, however, that neutropenia patients and comparison patients were similar in observed baseline characteristics and costs of non-neutropenia-related, care and that the differences in both total and neutropenia-related health-care costs were also similar. This indicates that such potential sources of bias probably did not substantially affect our findings.

In addition to these generic limitations of health-care claims data, several limitations specific to our study should be noted. First, an ICD-9-CM diagnosis code for neutropenic complications (i.e. neutropenia-related fever or infection) does not exist, and thus codes for neutropenia, fever, and infection were employed to identify hospitalizations for the events of interest. We hypothesized that, in many cases of neutropenia-related hospitalization, neutropenia would not be recorded as a diagnosis but fever or infection would, and thus we included codes for these conditions in our definition of neutropenic complications. In fact, of the 373 qualifying (i.e. initial) hospitalizations for neutropenic complications in our study, 53% had a primary or secondary diagnosis of neutropenia. While the strength of our definition of neutropenic complications is its sensitivity, it undoubtedly lacks specificity; however, we felt the former should be emphasized over the latter, and a similar algorithm has been employed in prior research [6, 13]. Secondly, for some cycles, a HCPCS level I code for administration of chemotherapy was present without any HCPCS Level II codes for specific chemotherapy agents. Not knowing whether the agent-specific codes had been omitted erroneously, the CPT code had been incorrectly entered, or chemotherapy had been obtained from another source (e.g. investigational drug study), we excluded all such patients and all associated cycles from our analysis. Observed differences between these patients (i.e. those excluded because of missing data on chemotherapy drugs) and patients in our study population were minor in nature. Thirdly, it was not possible to calculate the dose of chemotherapy received. Some patients may have received doses that were much more myelosuppressive than others. Fourthly, because we focused on hospitalizations for neutropenic complications as the index event, our results are not generalizable to neutropenic complications treated in an outpatient setting [15]. While such events (i.e. neutropenic complications requiring outpatient care only) have been found to be less expensive than those requiring inpatient care, their burden is still considerable totaling about one-quarter of the burden of inpatient events [16]. Fifthly, we may have underestimated the use of G-CSF therapy somewhat, since a unique HCPCS code for pegfilgrastim was not available between the date of its approval by the United States Food and Drug Administration (31 January 2002) and the end of calendar year 2002. Sixth, because neutropenia patients and comparison patients were matched on the number of chemotherapy cycles to ensure comparable durations of follow-up, our analysis does not incorporate the possible effects of chemotherapy discontinuation on health-care costs [17, 18]. Absent this matching criterion, it is possible that neutropenia patients would have had fewer cycles of chemotherapy, on average, than comparison patients, which could affect our estimates of costs; in fact, of the 197 patients who were hospitalized for neutropenic complications in their first cycle of chemotherapy, 46% had no evidence of subsequent receipt of chemotherapy. Seventh, while the estimated incidence of hospitalization for neutropenic complications in our study appears to be low compared with data from clinical trials, it is in fact consistent with another study employing data from a clinical practice setting (as in ours) [6]. Eighth, because patients, treatment patterns, and costs of care may vary across health-care settings and systems, caution should be exercised in generalizing the results of this study to other populations, as our study employed data from a single—albeit large—United States health-care organization. For example, our study population was comprised principally of cancer patients aged <65 years, and our results therefore may not be generalizable to older patient populations. Finally, amounts reimbursed (i.e. paid) for the provision of health-care services were used as a proxy for costs as the latter were not available in the study database. To the extent that reimbursed amounts do not reflect the true opportunity cost of resources used, our results may be upwardly or downwardly biased.

In summary, our findings indicate that neutropenic complications of myelosuppressive chemotherapy are costly. Prior research focusing on initial hospitalization only may have underestimated the economic cost of these complications by as much as 40%.

supplementary data

Supplementary data mentioned in the text is available to online subscribers at http://annonc.oxfordjournals.org
funding
Amgen Inc., Thousand Oaks, CA, USA.

references