Author's response to reviews

Title: Risk and Consequences of Chemotherapy-Induced Neutropenic Complications in Patients Receiving Daily Filgrastim: The Importance of Duration of Prophylaxis

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RESPONSES TO REVIEWERS’ COMMENTS:
Risk and Consequences of Chemotherapy-Induced Neutropenic Complications in Patients Receiving Daily Filgrastim: The Importance of Duration of Prophylaxis
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REVIEWER: WILLIAM RENWICK

Minor Revisions

Comment #1: Page 10/11 -Healthcare expenditure -is the $ value a mean or median?
Response: We have revised the text throughout the manuscript to specify that healthcare expenditures are reported in terms of mean values.

Comment #2: Page 11 -Re mortality figures -I understand the mortality data was only available from one of the databases but I think a comment should be made re the apparent differences in proportion of patients in the 3 categories with the data eg. D1-3 had only 119 of 243 patients (49%), D4-6 75 of 99 (75%) and D>7 34 of 40 (85%). There is a lot more data missing on the D1-3 category which could alter the numbers significantly. Is there any reason why one database had the bulk of patients getting >7 days of prophylaxis? This is an important, as the mortality data is the most instructive in the paper, so the data should be robust.
Response: We agree that these findings should be interpreted in light of the relatively high percentage of CINC patients in the filgrastim 1-3 days subgroup for whom mortality data were missing, and have added text (underlined below) to the Discussion (page 15) as follows:

“Hospital discharge disposition was available only in the MarketScan Database and information concerning LOS or paid amounts was missing for some hospitalizations. Moreover, we note that a disproportionately high percentage of patients receiving 1-3 days of filgrastim prophylaxis (vs. those receiving 4-6 or ≥7 days) who developed CINC requiring inpatient care did not have information available on discharge disposition, and thus the inpatient mortality findings must be viewed with caution.”

Discretionary Revisions

Comment #3: Page 11 -Re-the risks of CINC and odds ratios, the crude data show results crossing unity and therefore not significant. The adjusted analysis re the “narrow definition for CINC” then gives
significant results. Is the “narrow” definition, the taking out of admissions on the day of, or day after-the last filgrastim dose? I think some clarification is required re the definition as it changes the data to be significant as to not statistically significant.

Response: Methods employed to identify CINC were the same in unadjusted and adjusted analyses, including those focusing on the narrow definition of CINC as well as in other subgroup/secondary analyses (Table 3). We have added text (underlined below) to Methods – Statistical Analyses (page 9) clarifying this issue:

“...employing a narrow definition of CINC (identified using the diagnosis code for neutropenia only but otherwise the same algorithm for the broad definition as described above)…”

Differences in statistical significance between unadjusted and adjusted analyses are presumably due to controlling for systematic variation in patient characteristics between filgrastim prophylaxis groups in the latter. We have added a sentence to Results (page 11) addressing this issue as follows:

“We note that not all observed differences were statistically significant in unadjusted subgroup and secondary analyses, presumably due to the lack of adjustment for systematic differences in patient characteristics between prophylaxis subgroups.”

Comment #4 (general): the data may well be outdated with the advent of longer acting colony stimulating factors such as pegfilgrastim whereby the patient gets enough G-CSF for the whole cycle. It would be nice to know some comparison data re numbers of cycles of chemo now treated with daily filgrastim versus longer-acting forms, are they equal, is daily filgrastim no longer a significant component of supportive care?

Response: We agree that pegfilgrastim is (by far) the most commonly used CSF prophylactic agent among cancer chemotherapy patients, but note that filgrastim accounts for a small but important segment of the prophylactic market (e.g., ~11% in Weycker et al., AJCO 2011). We have added text to the Discussion (page 12) addressing this issue as follows:

“While pegfilgrastim—a longer-acting version of filgrastim that requires only a single dose administered subcutaneously once per chemotherapy cycle—is now (by far) the most commonly used CSF prophylactic agent in US clinical practice, filgrastim accounts for a small but important segment of the prophylactic market [14,16]. In the present study, 60,600 (45%) of the 135,921 adult cancer chemotherapy study subjects received CSF prophylaxis in ≥1 cycle during their chemotherapy course. Among the subgroup who received CSF prophylaxis, 91% received pegfilgrastim in ≥1 cycle and 9% received filgrastim.”

Comment #5 (general): I am surprised that any clinican would treat a patient with one day of prophylactic filgrastim, yet in this data set -29% of cycles of chemotherapy had only 1 day of prophylaxis! I cannot understand the clinical scenario where this would be appropriate and therefore it raises a question re the data, or the clinical practice.
Response: We agree that such a finding is surprising, given the indication for filgrastim and lack of definitive clinical evidence on the efficacy/effectiveness of abbreviated prophylaxis schedules. It appears, however, that this clinical practice phenomenon is real, as all of our previously published studies as well as several independent studies have found short prophylaxis courses with filgrastim (defined continuously in some studies, and as ≤3 days in others) to be relatively common place (Weycker et al., Ann Pharmacother 2006; Weycker et al., Clin Ther 2009, Weycker et al. AJCO 2011, Tan et al., CMRO 2011; Morrison et al., JMCP 2007; Cubells et al., Eur J Cancer Care 2012, Naismith et al., BMC Cancer 2013). We now briefly note the comparability of this finding to that from prior studies in the Discussion (page 12).

Minor Essential Revision

Comment #6: Page 11 cost data -The number of patients >7 is not stated as it was for the D1-3 and D4-6 patients ie after $13,165 (9,595 -17,144).

Response: Revision implemented as suggested.

REVIEWER: DAVID C. DALE

Comment #1: To interpret the paper, it would be useful to know the percentage of patients (by groups) treated with pegfilgrastim, since it is now the dominantly used myeloid growth factor. One could easily ask why these patients or subgroup of patients (roughly 4% of the total) were given filgrastim rather than pegfilgrastim.

Response: We agree, and have added text to Discussion (page 12) addressing this issue as follows:

“While pegfilgrastim—a longer-acting version of filgrastim that requires only a single dose administered subcutaneously once per chemotherapy cycle—is now (by far) the most commonly used CSF prophylactic agent in US clinical practice, filgrastim accounts for a small but important segment of the prophylactic market [14,16]. In the present study, 62,325 (46%) of the 135,921 adult cancer chemotherapy study subjects received CSF prophylaxis in ≥1 cycle during their chemotherapy course. Among the subgroup who received CSF prophylaxis, 91% received pegfilgrastim in ≥1 cycle and 9% received filgrastim.”

Comment #2: It is also not quite clear how many patients were given or took oral antibiotics. I understand that it is hard to know if oral therapies were taken even if prescribed. It is a common practice now to give the patient the prescription for an oral antibiotic and advise the patient to begin antibiotics at home if they have a fever. This practice confounds the analysis in the report but should be mentioned at least in the discussion.

Response: Because the route of administration was not of particular interest in this study, antimicrobial prophylaxis was defined to include both oral and IV agents. (Results are described in Table 1, and the method employed to identify antimicrobial prophylaxis use is described in Methods – Patient
We note, however, that the large majority of such use is oral, and now note this in Results (page 10) as follows:

“Antimicrobial agents—principally oral (~90%)—were concurrently used as prophylaxis in 6.7% of patients receiving 1–3 days of filgrastim prophylaxis, 7.5% receiving 4–6 days, and 7.5% receiving ≥7 days.”

We also have added text to the Discussion (page 15) addressing the limitation of using healthcare claims data to evaluate outpatient drug use, as follows:

“Finally, we note that it cannot be determined from outpatient pharmacy claims data whether drugs dispensed were actually taken, when they were taken, or how much was taken. For this reason, our characterization of antimicrobial prophylaxis use (principally oral) may be upwardly biased and differences in actual use across prophylaxis subgroups may confound the results of analyses. We also note, however, that the percentage of patients with filled prescriptions for antimicrobials was relatively low (and comparable) across filgrastim prophylaxis subgroups.”

Minor Comments

Comment #3: Are limitations of the work clearly stated? Yes.
Response: None required.

Comment #4: Is the question posed by the authors well defined? Yes.
Response: None required.

Comment #5: Are the methods appropriate and well described? Yes.
Response: None required.

Comment #6: Are the data sound? Yes. The analysis is based on very large data sets and the analytical methods are sound and sophisticated.
Response: None required.

Comment #7: Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.
Response: None required.

Comment #8: Are the discussion and conclusions well balanced and adequately supported by the data? Yes.
Response: None required.

Comment #9: Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes, the reference list is good.
Response: None required.

Comment #10: Do the title and abstract accurately convey what has been found? Yes.
Response: None required.

Comment #11: Is the writing acceptable? Yes, the paper is very well written.
Response: None required.