Comparison of Hospitalization Risk and Associated Costs Among Patients Receiving Sargramostim, Filgrastim, and Pegfilgrastim for Chemotherapy-Induced Neutropenia

Febrile neutropenia (FN) is a potentially life-threatening side effect of myelosuppressive chemotherapy; therefore, understanding the comparative effectiveness of colony-stimulating factors (CSFs) against FN is important for clinical practice. In a recent issue of *Cancer*, Heaney et al[1] presented a retrospective study suggesting that the risk of infection-related hospitalization may be lower for cancer chemotherapy patients who receive the CSF sargramostim (SAR) versus pegfilgrastim (PEG) or filgrastim (FIL). We believe serious design flaws in this study call into question their findings, and suggest that their results may not reflect the true comparative effectiveness of CSF agents.

For example, we believe the authors did not appropriately consider the timing of CSF use in a chemotherapy course (first vs later cycle) or the reason for CSF use (prophylaxis vs treatment), both of which may be associated with hospitalization risk. Systematic differences in these factors among CSF groups could confound results. The authors also defined follow-up differently across CSFs, which may have biased ascertainment of infection-related hospitalizations. For SAR and FIL, follow-up extended from the day of the initial administration to final dose (occurring $\leq$28 days from the previous administration). For PEG, follow-up included an additional 19 days after the final dose. Hospitalizations after final SAR or FIL administration were thus ignored, but counted (up to 19 days) after the final PEG administration. Moreover, the external validity of these findings was likely compromised by the use of a matched-cohort design (n = 990 SAR/FIL pairs, and n = 982 SAR/PEG pairs) that excluded data on the large majority of patients receiving CSF agents in clinical practice.[1]

In summary, we believe the findings of the study by Heaney et al should be interpreted with caution and that research employing a more appropriate study design[2] is warranted for examining the comparative effectiveness of CSF agents.

CONFLICT OF INTEREST DISCLOSURES

Funding for the preparation of this correspondence was provided by Amgen Inc to Policy Analysis, Inc. (PAI). We thank Linda Runft, from Amgen Inc, who assisted with the preparation of the letter. Richard L. Barron is an Amgen employee and owns Amgen stock.

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Derek Weycker, PhD
Policy Analysis, Inc (PAI)
Brookline, Massachusetts

Richard L. Barron, MS
Amgen Inc
Thousand Oaks, California

DOI: 10.1002/cncr.25239, Published online: March 30, 2010 in Wiley InterScience (www.interscience.wiley.com)

Reply to Comparison of Hospitalization Risk and Associated Costs Among Patients Receiving Sargramostim, Filgrastim, and Pegfilgrastim for Chemotherapy-Induced Neutropenia

We appreciate the concerns raised by Weycker and Barron regarding our study of the effects of sargramostim, filgrastim, and pegfilgrastim on hospitalization risks associated with chemotherapy-induced neutropenia,[1] but believe that their criticisms do not call into question the study's conclusions.

We agree that the risk of febrile neutropenia (FN) varies across multiple chemotherapy cycles, so we focused our study design on the use of colony-stimulating factors (CSFs) during the first few chemotherapy cycles, thereby capturing the period with the highest incident risk of FN. Our methodology also took into account the use of CSFs

for treatment versus prophylaxis because the adjusted hospitalization incidence rates controlled for the occurrence of a neutropenia diagnosis on the date of CSF initiation, reflecting CSF use for treatment rather than prophylaxis. The results found that pegfilgrastim indeed appears to be used more frequently for prophylaxis than sargramostim and filgrastim, and this potential confounding factor was accounted for in the regression model. Moreover, it is unlikely from a clinical perspective that sargramostim and filgrastim would be used differentially for treatment versus prophylaxis, thereby reducing the likelihood of biased estimates.

With regard to the duration of follow-up across the CSFs, Weycker and Baron appear to imply that the longer observation period penalizes pegfilgrastim (ie, assigns a higher incidence rate of hospitalization to pegfilgrastim). We believe that the longer therapeutic duration of pegfilgrastim compared with sargramostim and filgrastim necessitates a longer observation period and chose 19 days as the average real-life interval between pegfilgrastim administrations. Moreover, the use of patient-years of observation as the denominator for the incidence rate accounts for the longer therapeutic duration.

The matched cohort design was challenged because it excludes the majority of filgrastim and pegfilgrastim patients. Although there are many ways to control for potential confounders, matched cohorts are a well-established research design.[2,3] Indeed, when considering *all,* rather than matched pairs of CSF patients in the claims data, we found that filgrastim and pegfilgrastim patients tend to be younger (unpublished data). Matching thus reduced the likelihood of confounding due to differences in the age and gender distribution and permitted a better comparison. We agree that further study of this important topic is warranted, but we believe that our analysis and methodology appropriately considered real-world practice and experience.

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Mark L. Heaney, MD, PhD
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, New York

Edmond L. Toy, PhD
Analysis Group, Inc
Lakewood, Colorado

Francis Vekeman, MA
Analysis Group, Inc
Montreal, Quebec, Canada

DOI: 10.1002/cncr.25249, Published online: March 24, 2010 in Wiley InterScience (www.interscience.wiley.com)