Re: Personalized Medicine and Cancer Supportive Care: Appropriate Use of Colony-Stimulating Factor Support of Chemotherapy

In an editorial that accompanied our brief communication about the overuse of myeloid colony-stimulating factors (CSFs) in general practice (1), Dr Kuderer and Dr Lyman question our classification of high-risk chemotherapy regimens, our interpretation of clinical practice guidelines for CSF use, the validity of our febrile neutropenia (FN) ascertainment, and the interpretation of results (2).

Dr Kuderer and Dr Lyman suggest that we may have misclassified patients who received a regimen with a high risk of FN warranting prophylaxis with CSF as having received a lower-risk regimen. We based our categorization of the FN risk of chemotherapy regimens on the National Comprehensive Cancer Network (NCCN) guidelines from 2007, and the only high-risk regimen for lung or colorectal cancer at that time was topotecan (3). They suggest that we did not consider several additional regimens that the American Society of Clinical Oncology (ASCO) and recently updated European Organization for Research and Treatment of Cancer (EORTC) guidelines classify as having a high risk of FN (4,5). The ASCO guidelines include CAV (cyclophosphamide, doxorubicin, and vincristine) as a high-risk regimen, in contrast to NCCN, which classifies it as having an intermediate risk of FN (4,6). However, only one patient in our cohort received CAV, likely because it is not recommended as a first-line regimen and has substantially greater toxicity than other options for second- or third-line treatment of small cell lung cancer (6).

Two non–small cell lung cancer regimens (docetaxel/carboplatin and etoposide/cisplatin) that the EORTC classifies as high risk are considered low risk in both the NCCN and ASCO guidelines; multiple, large randomized studies report an FN incidence of less than 5% with these regimens (3). Among other regimens identified by EORTC as high risk (5), none are currently recommended by NCCN guidelines for treatment of small cell lung cancer (6), and several were from negative trials evaluating the benefit of dose-dense chemotherapy for small cell lung cancer. None of the patients in our cohort received any of these regimens (1). Therefore, misclassification is simply not a plausible justification for the high rate of CSF use we observed.

Our cohort was formed from patients diagnosed in 2005–2006 (1), which predates the more liberal guidelines cited by Dr Kuderer and Dr Lyman that sanction secondary CSF prophylaxis after the occurrence of other dose-limiting events or even primary prophylaxis when reduced dose intensity may compromise patient outcomes. However, unlike for lymphoma and breast cancer, the link between dose intensity and outcomes has not been made for lung or colorectal cancer, and therefore, this exception does not apply to our cohort. Furthermore, multiple randomized trials and a meta-analysis have failed to demonstrate any improvement in progression-free or overall survival with CSF support in lymphoma (7–16), breast cancer (17–19), or small cell lung cancer (20–25); cancers in which maintenance of chemotherapy dose and schedule could be expected to be most beneficial. Given the strong evidence that CSF support unfortunately does not improve progression-free or overall survival, even in the most chemosensitive of tumors, it is perplexing that the recent EORTC and NCCN guidelines recommend it. This has raised the concern that the process currently in place for developing oncology guidelines is subject to influence by manufacturers who stand to benefit from their recommendations (26).

Just as guideline members must disclose their potential conflicts of interest, so must editorial writers. The Journal published an erratum (2) reporting that Dr Lyman receives funding support from Amgen, Inc, the maker of filgrastim and pegfilgrastim. Dr Kuderer and Dr Lyman also question the accuracy of the toxicity data in Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) and suggest that FN may be underreported in our study because of “the absence of a specific International Classification of Diseases (ICD) code for FN and the need to use surrogates such as infection, neutropenia, or fever” (2). However, data on toxicity and other adverse events in the CanCORS study, including FN, were obtained from abstraction of the medical records of all of the patients’ inpatient and outpatient providers, including hospitalizations. Abstractors were instructed to record fever with neutropenia regardless of whether it resulted in a hospitalization. The overall incidence of hospitalization for fever, infection, or neutropenia among patients receiving chemotherapy ranges from 3% to 8% across population-based studies (27–32). The studies that use claims data to identify FN likely overestimate, rather than underestimate FN as suggested by Dr Kuderer and Dr Lyman, because claims-based definitions of FN typically include all hospitalizations for any infection during chemotherapy, regardless of whether or not they are related to neutropenia (27–30). Using an extremely broad definition of FN that included a fever or infection and neutropenia at any time during the cycle (not necessarily concurrently), Lyman et al. reported an 11% incidence of FN in an Amgen-sponsored prospective registry of patients receiving chemotherapy (33). The 7% incidence of FN identified by CanCORS is consistent with the other population-based studies, providing further assurance of the validity of our estimates.

Dr Kuderer and Dr Lyman suggest that the use of CSF for patients treated with low-risk chemotherapy regimens may have been based on patient and disease factors that increased the risk of FN. They claim that “in approximately half of the patients receiving intermediate- or low-risk chemotherapy regimens, the average personal risk of FN is 20% or greater because of these non–chemotherapy patient risk factors and should also prompt consideration of primary CSF prophylaxis based on the major guidelines” (2). We are unaware of data or studies that support this assertion. Moreover, we specifically investigated the extent to which CSF use in patients receiving chemotherapy regimens with a less than 20% risk of FN could be explained by patient factors, including age and comorbidity, as well as an episode of FN in a previous chemotherapy
cycle (1). Although severe comorbidity vs no comorbidity did increase the odds of receiving a CSF (odds ratio = 1.77, 95% confidence interval = 1.16 to 2.70, P = .01), age more than 65 years and an episode of FN in a previous cycle did not.

The stakes in this debate are high. In 2010, pegfilgrastim, the most commonly prescribed CSF, accounted for 5.2% of the $10.7 billion spent under Medicare Part B for drugs (34). In contrast to previous studies, including some supported by CSF manufacturers, our National Cancer Institute–supported study found that chemotherapy regimen and patient risk factors for FN did not explain much of the variation in discretionary use of CSFs occurring in general clinical practice. Therefore, until more definitive research clarifies the benefits of CSF use in patients who fall outside of current guideline recommendations, particularly those patients at below-average risk of FN, we maintain that more careful patient selection for CSF use can provide considerable cost savings without compromising patient outcomes.

References


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**Notes**

J. L. Malin was an employee of Amgen Inc, the manufacturer of granulocyte colony-stimulating factor (G-CSF; filgrastim), from 2005 to 2007, and has served as a consultant to Amgen on research studies.

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