DOI: 10.1093/jnci/djr195
Advance Access publication on June 13, 2011.

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

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Myelosuppression and neutropenic complications remain major dose-limiting toxicities of cancer chemotherapy resulting in increased morbidity, mortality, and costs (1,2). The major factors that are associated with the risk of mortality from febrile neutropenia (FN) include older age, cancer type and stage, documented infection, bacteremia, sepsis, venous thromboembolism, and the number of serious comorbid conditions (2–6). The risk for neutropenic complications, including FN, is greatest during the first cycle of chemotherapy when most patients are still receiving the full dose and schedule (7,8). When subsequent full-dose chemotherapy is continued on schedule without colony-stimulating factor (CSF) prophylaxis despite a previous neutropenic event, the risk of FN

remains high throughout the period of chemotherapy treatment (9). Initiation of the CSFs early in the first cycle of chemotherapy and continuation through all cycles of a chemotherapy regimen (primary prophylaxis) has been shown to substantially reduce the risk of FN as well as infection-related and early all-cause mortality, while decreasing the need for chemotherapy dose reductions and delays (10,11). Furthermore, most of the pivotal trials of primary prophylaxis with CSFs permitted secondary prophylaxis after a neutropenic event in the control arms, providing reasonable evidence that primary prophylaxis is superior to secondary prophylaxis (10). There are also increasing data from randomized controlled trials (RCTs) of patients with solid tumors and lymphoma on the potential value of CSF support of chemotherapy to improve overall survival (12).

The clinical practice guidelines for CSF use from the American Society of Clinical Oncology (ASCO) (13), the National Comprehensive Cancer Network (NCCN) (14), and the European Organization for Research and Treatment of Cancer (EORTC) (11), along with guidelines from the Infectious Diseases Society of America (IDSA) (15), recommend consideration of primary prophylaxis with CSF in patients at 20% or greater risk of FN. One of the risk factors for FN noted by the guideline panels is the specific chemotherapy regimen reported in RCTs, which is often classified as high risk (>20%), intermediate risk (10%–20%), or low risk (<10%) for FN (11,13,14,16,17). Unfortunately, patients in RCTs are often highly selected, and toxicities, including FN, are frequently underreported (18). In addition, chemotherapy dose intensity and the use of prophylactic CSF or antibiotics are infrequently reported in RCTs, making it difficult to assess the true burden of neutropenic complications associated with a chemotherapy regimen (18).

In addition to the specific chemotherapy regimen, a number of patient- and disease-specific factors are also associated with an increased risk of FN (2,19–22). The guidelines for CSF use from ASCO, NCCN, and EORTC note the importance of evaluating the patient's individual risk of FN and risk of mortality from FN when deciding the appropriate use of primary prophylaxis with a CSF (11,13,14). Although a number of risk factors for neutropenic events are considered by clinicians in assessing a patient's personal risk, only recently have formal clinical risk prediction models been validated for FN to aid clinical decision-making (21). The key factors associated with an increased risk of neutropenic events are: age older than 65 years, comorbid conditions, previous chemotherapy, type of cancer, type of chemotherapy, planned dose intensity, baseline leukopenia, liver function abnormalities, and renal dysfunction. 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 (11,13,14).

In this issue of the Journal, Potosky et al. (23) discuss the potential for both underuse and overuse of the CSFs in patients receiving cancer chemotherapy. The patterns of CSF use were examined in an observational cohort of lung and colorectal cancer patients maintained by the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS). The risk of FN was judged on the basis of a limited number of regimens illustrated in the NCCN guidelines for CSF use (14). The authors report primary CSF prophylaxis among 10% of patients on low-risk chemotherapy regimens, 18% on intermediate-risk regimens, and 17% on high-risk regimens. The authors conclude that all of the CSF primary prophylaxis in low- and intermediate-risk regimens and most of the secondary CSF prophylaxis was inappropriate. These observations along with the low CSF use in high-risk chemotherapy lead them to conclude that overall 96% of CSF use deviates from the guideline recommendations. The conclusions of this study (23), however, are based on the example of a single high-risk lung cancer chemotherapy regimen listed in the NCCN guidelines (14). Several additional examples of high-risk regimens for lung cancer are described by the ASCO (13) and the EORTC (11) guidelines, which were not considered by the authors. Importantly, all three guidelines also discuss the use of CSFs in patients receiving low- and intermediate-risk chemotherapy regimens when additional clinical risk factors for FN or mortality are present or when it is appropriate to maintain chemotherapy dose intensity (11,13,14). The overuse of CSFs reported in this study (23) is difficult to assess without accurate regimen risk classification, specific clinical data to evaluate the individual patient's risk, and information on the clinician's reasoning for choosing CSF support. Given the serious consequences of FN and the considerable regret if CSF prophylaxis is omitted inappropriately, clinicians may be more concerned about underuse of CSFs than overuse.

Potosky et al. (23) confirm the results of other investigators that the majority of growth factor support in practice is not for primary prophylaxis (24,25). Most of the CSF use appears to be for secondary prophylaxis following a neutropenic event, an FN treatment, or to facilitate full-dose intensity chemotherapy (12,24–26). Although the authors state that CSF use is mostly "discretionary" because of the low rates of FN recorded by them, the authors acknowledge that they were often unable to explicitly distinguish reasons for CSF use. As recording of toxicity data in the CanCORS database is dependent upon adequate documentation in the medical chart of each patient and accurate retrospective data abstraction, the validity of such toxicity reporting, including that for FN, is uncertain (27,28). In 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, accurate reporting of FN remains a substantial challenge for investigators and is likely underreported (18,29).

Potosky et al. (23) state that the NCCN guidelines recommend secondary use of a CSF only after an FN episode. However, the occurrence of other neutropenic complications as well as efforts to maintain chemotherapy dose intensity may lead an oncologist to consider secondary CSF prophylaxis in the appropriate setting (30). The NCCN guidelines also recommend secondary CSF prophylaxis after other dose-limiting neutropenic events, defined as a nadir count or day-of-treatment count that may otherwise lead to modification of the planned dose of chemotherapy (14). Likewise, the ASCO and EORTC guidelines recommend that when primary prophylaxis has not been given, secondary prophylaxis with a CSF should be considered in patients who experience a neutropenic complication in a previous cycle of chemotherapy or when reduced dose intensity may compromise treatment outcomes (11,13).

These recommendations are based on preclinical and clinical data suggesting that in responsive and potentially curable malignancies, maintaining chemotherapy dose and schedule are important considerations in reducing the risk of disease recurrence and improving long-term outcomes (26). Despite data for the importance of maintaining chemotherapy dose intensity in settings such as lymphoma and early-stage breast cancer, studies have demonstrated that many oncologists choose to reduce or delay chemotherapy delivery to lower the risk of myelosuppression (24,25,31–33).

Finally, Potosky et al. (23) suggest that the lower use of CSFs observed in Health Maintenance Organization (HMO) patients implies an overuse of CSFs in non-HMO coverage settings. However, an ASCO survey of oncologists concluded that HMO practices were more likely to prefer dose-reduction strategies over the addition of CSFs (31). Others have shown that there are racial and socioeconomic barriers to the use of prophylactic CSF, which is associated with reduced chemotherapy dose intensity in patients with early-stage breast cancer (34–36). Although prophylactic antibiotics are sometimes utilized in solid tumor patients to reduce costs, their routine use is discouraged by all major guidelines as they do not reduce mortality and are associated with the emergence of antimicrobial resistance (11,13–15). In the absence of specific reasons for CSF use, it is possible that the data reported here (23) are more consistent with the underuse of the CSFs in the HMO setting. Whereas the economic impact of these expensive agents has received considerable attention, the additional cost of the CSFs, when used appropriately according to the ASCO, NCCN, and EORTC guidelines, is offset in most settings by the reduction in FN hospitalizations and other medical costs (2,29,37–39).

Although there is little debate that both underuse and overuse of the CSFs occur in clinical practice, accurate estimates of the true magnitude and impact of such considerations remain elusive. What is clear is that there is a need for greater attention to chemotherapy-associated toxicities along with accurate prediction tools for the assessment of individual patient risks, including FN and its complications. Such tools could improve the evidence base for practice guidelines and aid clinicians in the selection of patients with cancer who are at an individual increased risk for FN, and therefore, appropriate candidates for the clinically effective and cost-effective use of the CSFs (40).

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Funding

American Society of Clinical Oncology (Young Investigator Award) (NMK); National Cancer Institute (RC2CA14041-01) (GHL,NMK); National Heart Lung and Blood Institute (1R01HL095109-01) (GHL,NMK).

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