

Improving the Management of Chemotherapy-Induced Neutropenia

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Our understanding of the problem of chemotherapy-induced neutropenia and our ability to manage it were revolutionized more than a decade ago with the advent of the

colony-stimulating factors G-CSF (filgrastim [Neupogen]) and GM-CSF (sargramostim [Leukine, Prokine]). Treatment-related neutropenia, as we have learned, has significant clinical consequences for the cancer patient, including life-threatening infections, prolonged hospital stays, and increased usage of intravenous antibiotics. It has also become clear that neutropenia is the primary dose-limiting toxicity of chemotherapy, which may, in turn, lead to dose reductions or delays in treatment that could compromise treatment effectiveness and potentially impact survival. In addition, neutropenia and its complications may impact patients' quality of life and increase anxiety and fatigue. The economic impact of febrile neutropenia on healthcare costs is considerable, and the cost of its treatment with colony-stimulating factors is not insignificant.

Thus, understanding the problem of chemotherapy-induced neutropenia as fully as possible and developing appropriate models for preventive strategies are critical to improving the clinical outcomes of cancer chemotherapy while reducing overall healthcare costs. We continue to learn more about the epidemiology of the problem, which patients are at risk, and how best to utilize the agents available. The development and approval of a second-generation hematopoietic growth factor, pegfilgrastim (Neulasta), have not only provided a more convenient approach to neutropenia management but have also led to renewed interest in the study of this important problem. Over the past

year, a number of important papers were presented at medical meetings that are reviewed in this supplement to *The Journal of Supportive Oncology*.

Chemotherapy-Induced Neutropenia in the Lymphoma Patient

Myelosuppressive chemotherapy regimens, such as the CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone) regimen, have been critical to improving the survival and cure rates for patients with non-Hodgkin's lymphoma. Retrospective analyses have suggested that delivering full-dose chemotherapy is associated with improved clinical outcome, although also associated with full-dose chemotherapy is increased myelotoxicity, particularly in older patients. The National Comprehensive Cancer Network's (NCCN) Cancer in the Elderly group has recommended that older patients with lymphoma receiving CHOP or CHOP-like chemotherapy also receive colony-stimulating factor (CSF) support during the first cycle of chemotherapy.

Thus, it is enlightening to look at the retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) Medicare data reviewed by Voelker and associates (page 40). In this large cohort of more than 35,000 elderly (age > 65 years) patients with non-Hodgkin's lymphoma, 22.4% were hospitalized for neutropenia, and 22.9% of those patients had more than one febrile neutropenic event. The majority of the events occurred during the first two cycles of chemotherapy, with the first cycle being the one of highest risk. These data clearly support the NCCN guidelines to utilize first-cycle CSF support to reduce some of the morbidity and potential mortality of febrile neutropenia in this patient population.

Bohlius and colleagues (page 42) performed a meta-analysis of randomized clinical trials for the Cochrane Hematologic Malignancy Group, evaluating the use of filgrastim and sargramostim in the treatment of malignant lymphoma. These studies showed that CSF prophylaxis significantly reduced the relative risk for neutropenia, febrile neu-

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tropenia, and infection compared with no prophylaxis. Although the authors could not identify any impact on complete response or overall survival, this large meta-analysis confirmed the utility of CSFs in reducing neutropenia-related complications in patients with non-Hodgkin's lymphoma across different age groups.

The studies included in this meta-analysis were primarily designed around neutropenia end points and were not designed to evaluate survival as a primary end point. However, more recent interest has focused on whether an improvement in treatment outcome could result from delivering chemotherapy in a more dose-dense fashion. The Norton-Simon hypothesis suggests that the cytoreduction produced by treatment with chemotherapy is also associated with a more rapid regrowth of the remaining cancer cells. Therefore, if one can shorten the interval between successive cycles of chemotherapy, this period of regrowth can be reduced and potential improvements in outcome may occur. Kloess and colleagues (page 44) administered CHOP every 2 weeks with growth-factor support in older patients with lymphoma. Prior studies demonstrated an improvement in tumor response rate and survival compared with an every-3-week schedule. This dose-dense therapy was accomplished with the use of filgrastim therapy for 10 days of each 2-week cycle. In the current report, the authors compared this schedule with a 7-day application of filgrastim. Although both schedules allowed chemotherapy to be delivered every 2 weeks, the briefer course of filgrastim was associated with lower neutrophil nadirs, delayed recovery, and more infections. The authors concluded that the 10-day filgrastim schedule was superior to a 7-day schedule in the delivery of dose-dense CHOP chemotherapy.

The Use of Pegfilgrastim in Lymphoma

The administration of pegfilgrastim as a single subcutaneous dose after chemotherapy has simplified the management of chemotherapy-induced neutropenia in patients receiving regimens that are administered every 3 weeks. Moore and colleagues in Columbus, Ohio, have presented preliminary data that pegfilgrastim can support an every-2-week R-CHOP chemotherapy regimen safely. In addition, Younes and associates at The University of Texas M. D. Anderson Cancer Center, Houston, have reported that a single dose of pegfilgrastim can be used to support ABVD (Adria-

mycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) chemotherapy in patients with Hodgkin's lymphoma (page 46). Primary prophylaxis consisting of 6 mg of pegfilgrastim given 24 hours after administration of ABVD every 2 weeks maintained the day 14 absolute neutrophil count (ANC) above 1,000/ μ L, and there was no progressive decline in the ANC with later cycles of treatment. Essentially, there were no delays in ABVD administration or reduction in dose intensity due to neutropenia, suggesting that pegfilgrastim was both safe and effective in this setting.

The importance of this observation relates to the current labeling of pegfilgrastim, in which the US Food and Drug Administration (FDA) recommends that chemotherapy not be administered within 14 days of pegfilgrastim. Every-2-week CHOP or ABVD would represent a 13-day interval. The FDA recommendation was based on a lack of clinical data with every-2-week chemotherapy regimens at the time of initial approval. There was also concern that if this long-acting CSF was still present from a prior treatment cycle, there might be an increased number of dividing hematopoietic cells at the time of administration of cytotoxic chemotherapy, which could result in a paradoxical increase in myelosuppression. It is quite reassuring that this was not seen in the study reported by Younes and associates.

Further support for the safety of every-2-week pegfilgrastim can be seen in the study by Yang and co-workers (page 48). In this study, a retrospective analysis was performed of pegfilgrastim serum concentrations from day 10 to day 12 post administration. Results of this analysis showed that only 6% of the patients on day 11 and 0.2% of the patients on day 12 still had a pegfilgrastim serum concentration greater than the EC_{20} , the lowest pegfilgrastim serum concentration able to elicit a meaningful biologic response. These data therefore suggest that pegfilgrastim could be used safely in dose-dense chemotherapy regimens that are administered every 2 weeks. Further studies are being conducted to expand on these observations.

Chemotherapy Delivery and CSF Use in Breast and Lung Cancer

The importance of delivered dose intensity of chemotherapy has been best studied in women with early-stage breast cancer receiving adjuvant treatment. Agboola and colleagues in the ANC Study Group performed a retrospective survey of more

Management of Chemotherapy-Induced Neutropenia

than 1,200 community oncology practices, including more than 20,000 patients treated between 1997 and 2000 (page 50). More than half of the patients (58%) received an average relative dose intensity of less than 85%. This was the threshold associated with poor outcomes in the pivotal retrospective work by Bonadonna and colleagues. The factors that placed patients at higher risk for a reduced relative dose intensity included older age, higher body surface area, and receiving CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) or CAF (cyclophosphamide, Adriamycin [doxorubicin], and 5-fluorouracil) chemotherapy (page 52). Although first-cycle use of CSFs was uncommon during the time period studied, CSF prophylaxis was associated with an increased likelihood of the patients receiving full dose intensity. In addition to the abstracts presented in this journal, the authors' work was published in the December 15, 2003, issue of the *Journal of Clinical Oncology*.

Although multiple factors likely account for the reduced dose intensity of adjuvant chemotherapy in the community setting, clearly more prospective studies are necessary to understand the variables involved and to demonstrate prospectively whether CSF-supported delivery of full dose intensity in the adjuvant setting will, in fact, lead to better outcomes in breast cancer patients.

To address whether or not delivery of chemotherapy with filgrastim in the community setting does lead to delivery of full-dose chemotherapy, Epstein and colleagues (page 54) reported the results of a multicenter open-label phase IV clinical trial of filgrastim used in a variety of tumor types, including breast cancer, lung cancer, ovarian cancer, non-Hodgkin's lymphoma, and other tumors. A total of more than 3,000 cycles of chemotherapy were evaluated, with a median use of 11 days of filgrastim therapy for each chemotherapy cycle. A total of 780 pediatric and adult patients were included. The analysis showed that 91% of chemotherapy cycles were given on time and that 90% were given at full dose. This large community-based trial would suggest that the use of growth factors can improve chemotherapy dose delivery in the community oncology setting. Prospective studies are warranted to look at whether these improvements in dose delivery are also associated with improvements in treatment outcomes.

In an attempt to address whether CSF-supported chemotherapy could in fact improve treatment outcomes, Kasymjanova and colleagues conduct-

ed a single-center retrospective comparative analysis of patients with non-small cell lung cancer receiving carboplatin (Paraplatin)-based chemotherapy. Of the 127 patients whose charts were reviewed, 81 (63%) experienced grade 3 or 4 neutropenia (page 56). Forty-two patients with severe neutropenia or active infections who subsequently received filgrastim had a longer median survival than patients who did not receive CSF support. The two groups of patients were balanced for disease stage, performance status, weight loss, and dose-intensive chemotherapy. There are obviously multiple explanations for this observation, and prospective studies would be needed before any conclusions could be made.

Meanwhile, Riedel and colleagues at Duke University Medical Center reported the results of a phase II open-label prospective clinical trial of pegfilgrastim in support of dose-dense carboplatin/vinorelbine treatment of patients with thoracic malignancies (page 58). Again, as in the study reported by Younes et al, discussed earlier, pegfilgrastim was safely administered with a 13-day interval between the growth factor and subsequent chemotherapy. Febrile neutropenia was rare. Chemotherapy dose reductions did occur in this population due to comorbidity and delayed administration of pegfilgrastim until day 9, the day following the second injection of vinorelbine in each cycle. This study documents the ability to deliver dose-dense chemotherapy even in patients with thoracic malignancies, but larger trials will be needed to determine whether treatment outcome is improved.

Economic Impact of Growth Factors

The availability of pegfilgrastim has provided great convenience for patient and provider alike by offering a single injection versus prolonged daily therapy. The economic impact of this benefit was evaluated by Kaneshiro and colleagues in a retrospective review of physicians' prescribing practices at VA Long Beach (California) Medical Center (page 60). Pegfilgrastim had a \$79 per patient advantage in drug cost over filgrastim (5 $\mu\text{g}/\text{kg}$ per day) when the latter was administered for 10 days at the 480 $\mu\text{g}/\text{vial}$ dose. Based on the authors' analysis, 20% of patients could have been switched to pegfilgrastim without an increase in drug cost. The authors commented on, but did not calculate, the indirect cost to the patient caregiver of repeated daily administration of filgrastim versus a single visit to the clinic to receive pegfilgrastim.

The economic impact of pegfilgrastim use was also evaluated in a multicenter retrospective pharmacoeconomic analysis by Lyman and colleagues of the ANC Study Group (page 62). In their analysis, the cost minimization threshold for first-cycle risk of febrile neutropenia for no pegfilgrastim use versus universal use was 23% above which universal use was associated with lower overall costs. This threshold is remarkably similar to the level outlined in the prior SEER data reported by Voelker and co-workers. This suggests that the targeted use of pegfilgrastim in older patients with non-Hodgkin's lymphoma who are at increased risk of febrile neutropenia during the first cycle of chemotherapy can reduce overall healthcare costs. Assessing a patient's individual risk for neutropenic complications should prove to be a better strategy for the cost-effective use of hematopoietic growth factors compared with a fixed-risk threshold.

Effect of Neutropenia on Quality of Life

Until recently, quality-of-life assessments had not been performed in patients with neutropenia, the presumption being that if one were able to reduce febrile neutropenia and hospitalization, quality of life for these patients would undoubtedly improve. However, what about the potential impact of neutropenia per se on quality of life? Calhoun, Cella, and colleagues conducted quality-of-life assessments in chemotherapy-naïve patients undergoing treatment for breast or ovarian cancer (page 64). Patients who experienced neutropenia-induced chemotherapy delays exhibited a significant effect on their psychological well-being in terms of tension, depression, and anger, which negatively impacted on their quality of life.

In a second study, Ashley and colleagues interviewed patients receiving chemotherapy about their quality of life at the time neutropenia occurred (page 66). Fatigue was the most common

physical symptom and was associated with interference in the patients' daily routines. Although larger trials will be necessary to sort out the impact of chemotherapy per se from other comorbidities, such as anemia, this study corroborates what our patients often tell us—they feel poorly when their “counts are low.” In addition to confirming the presumptive relationship between neutropenia and impaired quality of life and physical functioning in a larger cohort of patients, it would be interesting to explore the biological basis for such a relationship. Could it be related to endogenous cytokine production or to other interactions between the hematopoietic and central nervous systems? This is one more area of study that may help us understand more fully the basis for fatigue in our cancer patients.

Future Directions

In this overview, we focused on the epidemiology of chemotherapy-induced neutropenia and its impact on febrile neutropenia, planned chemotherapy dose delivery, and treatment outcomes and on the impact of hematopoietic growth factors in these situations. Although much still has to be learned in all of these areas, the results of the study reported by Devine and colleagues (page 68) remind us that we have even more to learn about the broader potential uses of these growth factors in other areas of oncology and medicine. In their study, leukapheresis products were analyzed for dendritic cell content after mobilization with filgrastim or sargramostim, alone and in combination. Although no significant differences were seen in the dendritic cell content, the incidence of graft-versus-host disease was lowest in patients receiving sargramostim alone. Further studies of these cytokines are needed to understand better their impact on the immune system to optimize use of these agents for immune recovery in cancer patients.