

Update on Neutropenia and Myeloid Growth Factors

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This issue of *The Journal of Supportive Oncology* reviews several important abstracts dealing with neutropenia and neutropenia management, which were selected from the 2006 meetings of the American Society of Clinical Oncology (ASCO), the Oncology Nursing Society (ONS), and the American Society of Hematology. Although the body of this research covers a wide range of clinical issues, the abstracts themselves can be grouped into three general categories. The first group focuses on the efficacy of pegfilgrastim (Neulasta), supported with data from large prospective clinical trials. The second category looks at the health economics of febrile neutropenia, as well as the importance of practice guidelines for the management of chemotherapy-induced neutropenia. The last group of abstracts focuses on the vital area of patient risk assessment before initiation of chemotherapy in an attempt to better identify high-risk versus low-risk populations for proper application of their appropriate guidelines.

Efficacy of Pegfilgrastim

Ozer et al (page 38) presented the results of a large, community-based prospective study that examined the impact of first- and subsequent-cycle use of pegfilgrastim on neutropenic events in patients receiving myelosuppressive chemotherapy. Over 2,000 patients were enrolled, with more than a third of patients over the age of 65 years; more than 50% had advanced-stage disease, more than 25% had significant comorbidity, 23% had received prior chemotherapy, and 17% had received prior radiotherapy. In this group of patients, the incidence of febrile neutropenia was 1.7% in the first cycle and 3.5% across all cycles of treatment. It is unclear what proportion of these patients would have been eligible for myeloid growth factors by current guide-

lines from the National Comprehensive Cancer Network (NCCN), ASCO, and the European Organisation for Research and Treatment of Cancer (EORTC).¹⁻³ However, the low incidence of febrile neutropenia in this elderly, advanced-stage population with significant comorbidity and a history of therapy is impressive and suggests that this agent can minimize neutropenic complications across a broad range of tumor types and chemotherapy regimens in the community setting.

Noga et al (page 36) evaluated the role of pegfilgrastim in a subset of patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) from the same community study, providing a more homogeneous population and chemotherapy regimens. In total, 325 patients with NHL and 46 patients with HL were included in the primary analysis set. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-like regimens were the most commonly used regimen for NHL, and ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) was the most commonly used regimen for HL.

Despite the use of regimens associated with neutropenia and febrile neutropenia, the incidence of these complications was low in both populations, with only 37% of NHL patients and 4% of HL patients experiencing grade 3/4 neutropenia in cycle 1. In the HL population, there were no episodes of febrile neutropenia, although 4% of patients did require hospitalization in cycle 1 related to neutropenia. In the NHL group, 8% of the patients had cycle 1 febrile neutropenia and 9% of the patients required hospitalization. Again, without a control group, the magnitude of reduction in neutropenic events cannot be quantitated, but the low overall incidence in this population, where neutropenia and febrile neutropenia are common, is another demonstration of pegfilgrastim's ability to minimize neutropenic complications.

Another study did provide further data regarding primary prophylaxis with pegfilgrastim in NHL patients undergoing chemotherapy. In this trial by Pettengell and colleagues (page 40), 282 patients

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Neutropenia and Myeloid Growth Factors

were identified from three separate prospective clinical trials and evaluated in a retrospective integrated analysis. The overall incidence of febrile neutropenia across all cycles was 15%, with half of those events occurring in the first cycle of treatment. As in other series, the risk of these events was higher in the population older than 65 years versus those younger than 65 years. Compared with historic controls, and with the benefit of such a large data set, first-cycle use of pegfilgrastim appears to be effective in reducing the overall rate of febrile neutropenia in the lymphoma population receiving CHOP and CHOP-like chemotherapy.

The take-home message from these studies is that pegfilgrastim can be effective across a range of patient populations, including populations that often are not included in clinical trials, such as elderly patients or patients with advanced disease. However, despite the clinical efficacy of pegfilgrastim in unselected populations, it is important to continue using myeloid growth factors according to practice guidelines. Although many of the patients in the Ozer community study and perhaps most of the patients in the two lymphoma studies would have qualified for first-cycle use of myeloid growth factors, there are also low-risk populations in these studies for whom myeloid growth factors are not indicated in the first cycle.

Economics and Practice Guidelines

This brings us to the area of cost effectiveness. As the previous studies have outlined, myeloid growth factors clearly are clinically effective across a range of patient risks. However, the guidelines committees suggest a threshold of 20% risk of febrile neutropenia before routinely using first-cycle prophylaxis.¹⁻³ The NCCN, EORTC, and ASCO committees also agree that patients who are at lower risk of febrile neutropenia based on the chemotherapy regimen alone can be considered for first-cycle prophylaxis if they have additional patient risk factors that would likely place them at this 20% risk or greater. The use of the 20% threshold not only offers a well-documented clinical benefit but also is associated with cost minimization in the use of myeloid growth factors.⁴

In this setting, it is instructive to look at the abstract by Weycker et al (page 44). This study is not focused on the cost of myeloid growth factors per se but instead centers on the cost of chemotherapy-related febrile neutropenia. From a large, US healthcare claims database, patients who de-

veloped febrile neutropenia were compared with those who did not in a case/control fashion. Febrile neutropenia-related charges amounted to more than \$40,000 per patient with febrile neutropenia compared with less than \$4,000 for controls. All other charges were similar between groups at approximately \$32,000. The overall cost of care for chemotherapy patients who had febrile neutropenia was more than twice that of patients who did not have febrile neutropenia, with all of that difference in cost related to febrile neutropenia and its management. Thus, the costs of the myeloid growth factors always need to be considered in the context of the overall economic impact that neutropenia and febrile neutropenia have in this population. At present, the best way to minimize those costs is to effectively implement practice guidelines.

Although the NCCN, ASCO, and EORTC guidelines have been well publicized and are consistent with each other, it is quite a different issue to implement these guidelines in daily practice. In this regard, Maxwell and colleagues (page 46) discussed the implementation of practice guidelines “from paper to practice,” highlighting the important role that nurses play in the implementation of clinical practice decisions—particularly in the arena of supportive care—working as part of the healthcare team. Individual clinic, office, and hospital-based practices have been able to incorporate algorithms into their workflow for management of emesis, pain, and other important supportive care needs for the cancer patient receiving chemotherapy. The same broad-based, multidisciplinary approach will be critical to the successful implementation of these guidelines for neutropenia management.

As one part of the current practice guidelines,¹⁻³ myeloid growth factors are currently recommended not to be initiated until the day after cytotoxic chemotherapy is completed. Trials with filgrastim (Neupogen) and sargramostim (Leukine) demonstrated that their daily administration with cytotoxic chemotherapy reduced the benefit of these agents. The hope, in the era of pegfilgrastim, was that perhaps a single-dose agent could be administered safely on the same day as chemotherapy. Belani et al (page 30) performed a randomized, double-blind, phase II study in patients with non-small cell lung cancer looking at same-day versus next-day administration of pegfilgrastim with carboplatin and docetaxel (Taxotere). In this particular study, there was not a significant difference in neutropenia rates between the two groups. However, the duration of

neutropenia is generally brief with taxane-based regimens, so the ability to distinguish a difference in the duration of neutropenia might be difficult in such a small sample size. Furthermore, in two other previously reported studies in breast cancer and lymphoma,^{5,6} same-day administration of pegfilgrastim resulted in an increase in the duration of neutropenia compared with next-day administration.

This finding is consistent with the simultaneous exposure of hematopoietic progenitor cells to cytotoxic chemotherapy and the stimulatory effects of colony-stimulating factors, resulting in increased cell destruction in the short term. On the other hand, there is a large safety database, both in terms of short-term and long-term safety, with the initiation of myeloid growth factors the day after chemotherapy. Therefore, even though it is convenient for the patient and provider to administer same-day myeloid growth factor and chemotherapy, the current data clearly do not support this approach and current practice guidelines should be followed.

Risk Assessment

To enhance both the clinical and cost effectiveness of myeloid growth factors, it is important to refine models of patient risk and to incorporate those risk factors into clinical practice. In a prospective randomized trial reported by Biron et al (page 32) the investigators used a pretreatment lymphocyte count of less than 700/ μ L as a way to identify patients at risk for febrile neutropenia and then prospectively evaluated whether first-cycle use of filgrastim resulted in a reduction in febrile neutropenia compared with a secondary prophylactic strategy. In this study, a pretreatment lymphocyte count of less than 700/ μ L and use of “high-risk chemotherapy” were associated with a 38% rate of febrile neutropenia in the group who did not receive primary prophylaxis. By contrast, the group randomized to receive first-cycle prophylaxis with filgrastim had a 25% rate of febrile neutropenia, or approximately a 34% reduction. Because of the small sample size in this phase II study ($n = 137$), statistical comparisons should be limited. However, the authors have nicely demonstrated the potential value of specific laboratory tests such as lymphocyte count in a prospective trial. The authors have also confirmed the benefit of an intervention strategy in this high-risk population.

The last abstract in this group comes from Doyle and colleagues (page 34), who reported on

the role of the oncology nurse in prechemotherapy neutropenic risk assessment. In this group, a risk-assessment tool was developed based upon the NCCN guidelines and was completed by the clinic nursing staff for all new patients beginning chemotherapy in the cancer care clinic at the Puget Sound VA Medical Center in Seattle, Washington. After implementation of this risk-assessment tool into clinical practice, the number of hospitalizations for febrile neutropenia dropped by 78%, from 9.7% in 2004 to 2.1% in 2005. This reduction corresponded to an increase in proactive use of growth-factor support in an evidence-based approach. This group should be congratulated for such an excellent demonstration of “closing the loop” from clinical trials to practice guidelines to implementation in one’s own practice setting. For those of us in the clinical trial and guidelines arena, it is extremely gratifying to see such results and their impact on patient care.

These final steps of guideline implementation and outcomes assessment of that implementation are critical if we are going to practice the quality medicine we preach. Thanks to the example of the nurses at the Puget Sound VA, we hopefully will continue closing that loop.

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