Chemotherapy-induced neutropenia (CIN) is the primary dose-limiting toxicity in patients being treated for cancer. The substantial toll of CIN includes febrile neutropenia (FN), hospitalization, infection, early mortality, increased medical costs, decreased quality of life, and the potential for diminished long-term survival due to chemotherapy dose reductions and delays.[1]

The advent of colony-stimulating factors (CSFs) such as filgrastim (granulocyte colony-stimulating factor [Neupogen]) and sargramostim (granulocyte-macrophage colony-stimulating factor [Leukine]) more than a decade ago revolutionized the management of CIN. Supportive therapy with CSFs reduces the rates of FN, hospitalization, and use of intravenous anti-infectives, and helps maintain the relative dose intensity of chemotherapy. The more recent availability of pegfilgrastim (granulocyte colony-stimulating factor [Neulasta]), a long-acting CSF, has further advanced the management of CIN by making once-per-cycle administration possible.[1]

More accurate quantification of the benefits of CSF therapy—both clinical and economic—has resulted in further progress. A decade ago, Lyman and colleagues developed a cost-minimization model suggesting that the routine prophylactic use of filgrastim in the first cycle became cost-neutral in patients in whom the predicted risk of FN was 40%. That result was based on cost data from a single institution and on clinical data that demonstrated a 50% reduction in the rate of FN among patients with an expected historical FN risk of 40%.[2]

Newer data have made it possible to refine that original cost-minimization model—with substantial changes to its implications. More complete hospital data have led to a substantial upward revision to the estimated cost of a single episode of FN. In addition, pegfilgrastim has recently demonstrated enhanced results in patients in whom the risk of FN is less than 20%, reducing the risk of FN by 94%, hospitalization by 93%, and use of intravenous anti-infectives by 80%.[3] Based on these data, the revised model now suggests that routine use of first-cycle pegfilgrastim becomes cost-neutral when the risk of FN is 15%.[4]

Progress has also been made in our ability to identify individual patients at increased risk for neutropenic events. It is clear that the risk of CIN, FN, and mortality associated with FN is highest in the first cycle of chemotherapy.[5] It is therefore necessary to improve our understanding of baseline risk factors such as age, comorbidities, underlying disease activity, and the planned regimen. More to the point, it will be crucial to incorporate a refined understanding of these factors into risk assessments that can be performed prior to the beginning of cycle 1, so that CSF therapy can be administered to appropriate patients at the time of highest risk. [1]

The Guidelines for Myeloid Growth Factors in Cancer Treatment, recently released by the National Comprehensive Cancer Network (NCCN), unite these multiple threads of progress into a single framework.[6] The NCCN guidelines incorporate individual risk factors to a degree not previously seen. In addition, consistent with the recent pegfilgrastim clinical data, as well as other data demonstrating benefit with filgrastim at risk levels between 20% and 40%, the guidelines recommend the routine use of CSF in the first and subsequent cycles in patients with a greater than 20%, “high” level of neutropenic risk. For patients with expected neutropenic risk of 10% to 20%, the guidelines recommend consideration of treatment intent. Patients receiving potentially curative chemotherapy or in whom prolonged life is the goal may warrant proactive CSF use as a safeguard against unplanned dose reductions and delays, whereas patients receiving palliative treatment may not.[6]
Colony-Stimulating Factor Use in the Context of Refined Risk and Benefit Assessments

The greater consideration of risk factors and treatment intent has promising implications in patient groups who are at increased risk for neutropenic events and are therefore often undertreated. It has been suggested, for example, that the lower rates of clinical response to chemotherapy sometimes observed in elderly patients are due in part to physicians routinely treating these patients with less-than-full-dose chemotherapy, with dose reductions often planned from the outset of chemotherapy.[7] An alternative approach is to assess elderly patients for increased neutropenic risk proactively and administer CSF where appropriate, in order to treat with full-dose chemotherapy and thereby improve outcomes in a greater number of patients.[8]

The papers that follow present these ongoing developments in three parts. Dr. Howard Ozer (pages 11-15) reviews the negative impact of CIN and data demonstrating that the highest risk of CIN is in the first cycle of chemotherapy. Dr. Michael Rader (pages 16-21) reviews data supporting the clinical efficacy of filgrastim and pegfilgrastim, as well as recent cost-minimization analyses demonstrating cost-neutrality in patients in whom the risk of FN is less than 20%. Finally, I will review (pages 22-28) the known risk factors of serious neutropenic events, present the new NCCN guidelines on the use of CSF therapy, and discuss the implications of this new information for patient groups that have been traditionally undertreated, such as the elderly.

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Disclosures:
The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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