

## Moving Forward With Myeloid Growth Factors

Since the initial approval of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) for clinical use in 1991, our understanding of these agents has grown substantially. Laboratory investigation, clinical trials, and outcomes research have all been of pivotal importance to our knowledge base. Equally important has been the parallel process of guidelines development, initially through ASCO and subsequently with ESMO and other societies.

Over the past decade, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) have provided the most frequent updates and revisions for the clinical practitioner to help integrate evidence for use with the realities of clinical practice. For example, the NCCN Guidelines Panel initially established the febrile neutropenia threshold for use of myeloid growth factors at 20%; this standard has now been adopted by virtually all other guidelines committees. Moreover, it was the NCCN Panel who stressed the importance of assessing febrile neutropenia risk not only based on chemotherapy regimen but also considering individual patient factors that substantially influence this risk.

These elements are important because clinical trials historically underreport toxicities such as febrile neutropenia unless these data are prospectively collected through preplanned analyses. In addition, patients who enroll in clinical trials are not always representative of the general cancer population, who are often older and have comorbid disease. Both of these things place them at higher risk for developing febrile neutropenia from chemotherapy.

Electronic health records and outcomes research have helped us better identify the magnitude of this problem at the population level, but we have not fully resolved or refined risks at the individual patient level. The work of many colleagues referenced in the NCCN Guidelines for Myeloid Growth Factors (in this issue; to view the most recent version of this guideline, visit [NCCN.org](http://NCCN.org)) has helped considerably in establishing models of patient risk, but broad application of these strategies remains to be implemented.

Thus, the clinician is left with general guidelines, including the NCCN Guidelines, which must be implemented for individual patients. At the same time, clinicians must be appropriately conscious of cost concerns and possible overuse. Further complicating the decision process is that the highest risk of febrile neutropenia is in the first cycle of cytotoxic therapy. Therefore, “watch and wait” is often not a good strategy.

Importantly, the expense of hospitalization and intravenous antibiotics incurred with neutropenia is substantial. The impact on the patient may also be substantial—particularly for older patients with significant comorbid disease—with resultant complications of infection, pneumonia, delay in therapy, and risk of mortality. So the stakes remain high for all of us to get this right. The goal of the NCCN Guidelines Panel for Myeloid Growth Factors is, in fact, to help in that process.

The NCCN Guidelines for Myeloid Growth Factors, Version 2.2013 (in this issue), include a number of revisions from previous versions. Specifically, the reader should note that we have added a section describing a new myeloid growth factor, tbo-filgrastim, as an alternative to the other daily myeloid growth factors currently available. The FDA approved this agent based on 3 randomized clinical trials summarized in the NCCN Guidelines. The trials concluded that tbo-filgrastim is noninferior to filgrastim regarding the incidence of febrile neutropenia, with similar toxicities and pharmacokinetic and pharmacodynamic profiles.



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Of note, the FDA approved this agent based on a biologic license application because the process of approval for biosimilars is still under review. In a related article in this issue, Drs. Bradford R. Hirsch and Gary H. Lyman address biosimilars in oncology more broadly. The authors discuss models of the possible economic impact of tbo-filgrastim versus filgrastim versus biosimilar filgrastim, based on a European analysis. What clinical and economic impact will occur in the United States as this agent becomes available is still to be seen. However, a broader menu of agents will certainly stimulate more competition, more interest, and more research, all of which will ultimately be good for the field of oncology and for our patients.

Another new section of the NCCN Guidelines this year is our initial recommendations regarding the use of myeloid growth factors in the hematopoietic cell transplant setting. I am grateful to Dr. Pamela Becker and her subcommittee, who helped formulate these initial guidelines. We look forward to feedback from the NCCN Member Institutions and the guidelines readership for comments and suggestions on how we might further improve this section, and the guidelines overall.

Much has been written about evidence-based versus consensus-based guidelines. In my mind, there is clearly a role for both, building on the evidence base with consensus recommendations from the expert panel. We all recognize the potential risks of consensus-based guidelines if they are not firmly rooted in evidence; however, in many clinical situations, evidence often stops short of providing useful guidance. The NCCN Guidelines process allows correction and refinement of both the evidence base and consensus base from broad input, providing an ideal balance on an ongoing basis.

Finally, I have had the privilege of serving as Chair of the NCCN Myeloid Growth Factors Panel since its inception, and have been continuously impressed by the knowledge, thoughtful decision-making, and commitment of the members of the panel to our process of continual improvement. The physicians and pharmacists on our committee, with support from an outstanding NCCN administrative staff, provide an impressive range of expertise across all the areas of hematology-oncology so relevant to myeloid growth factors and their proper use. I would like to take this opportunity to personally thank all of the panel members for their ongoing efforts.