Advances in the Management of Chemotherapy-Induced Neutropenia

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It has been more than 15 years since the initial approval of myeloid growth factors to reduce febrile neutropenia in cancer patients receiving myelosuppressive chemotherapy.[1] As with other novel therapeutics, the approval of filgrastim (Neupogen) did not mark the end of research in this area, but rather the beginning.

Guideline Evolution
Shortly after the approval of filgrastim and sargramostim (Leukine), the American Society of Clinical Oncology (ASCO) convened a panel of experts to develop practice guidelines around their appropriate use.[2] These guidelines have been updated several times, with the most recent update in 2006.[3] In addition, the European Organisation for Research and Treatment of Cancer (EORTC) also developed guidelines around the appropriate use of myeloid growth factors in 2006.[4] Preceding both of these groups, the National Comprehensive Cancer Network (NCCN) developed clinical practice guidelines for myeloid growth factors in 2005.[5]

While all three of these guidelines panels have somewhat different methodologies, all three reached the same recommendations. Primary prophylaxis is indicated in the first cycle of chemotherapy in patients with a risk of febrile neutropenia or other serious neutropenic complications at a threshold of 20% or greater. At risk thresholds below 20%, the groups have some slightly different algorithms, but all would agree that individual patient risk factors should be taken into account in determining whether primary prophylaxis should be used. In addition, the NCCN specifically would incorporate into the decision process whether the intent of therapy is curative, life-prolonging, or palliative. What led to this significant change in guidelines recommendations from previous ASCO guidelines that required a 40% risk or greater? The answer can be found in the articles in this supplement.

Drs. Al-Kali and Ozer nicely review the background of the evolution of the colony-stimulating factor (CSF) guidelines over the past 12 years. In addition to the clinical trial data showing benefit at lower rates of febrile neutropenia, they also address the impact that cost has had on these guidelines. With the increasing costs of hospitalization that threshold has also been lowered. The authors nicely discuss the primary action of CSFs in the reduction of the duration of neutropenia and contrast that with the role of prophylactic antibiotics. The latter have been documented to reduce the rate of fever/infection, but without impacting neutrophil recovery and with the associated potential increased risk of drug-resistant organisms. Clearly the two strategies of CSFs and prophylactic antibiotics are different; future efforts need to address how these approaches can be complimentary. The authors also address the change in the way we think of supportive care for the patient receiving myelosuppressive chemotherapy. In the past, with the "40% rule," almost all patients receiving standard chemotherapy regimens fell below this threshold of risk. Therefore, the myeloid growth factors were reserved for secondary prophylaxis in patients who had experienced a prior episode of febrile neutropenia. An initial episode of febrile neutropenia was considered "an acceptable toxicity." Obviously, over the past decade we have become aware of the faulty nature of this logic. As the authors point out, this reactive approach ignores the high first-cycle event rate of febrile neutropenia, the impact of febrile neutropenia on subsequent dose reductions and delays that may adversely influence overall treatment outcome, and lastly and most importantly, the exposure of cancer patients at risk for what may be a life-threatening or fatal toxicity of chemotherapy.

Growth Factors in Dose-Dense Treatment
In addition to the use of myeloid growth factors to reduce the toxicity of myelosuppressive chemotherapy, Dr. Burstein addresses the role of these agents for dose-dense treatment. By definition, dose-dense therapy involves giving full doses of chemotherapy more frequently than would standardly be administered. Most chemotherapy regimens are currently administered every 3 weeks, not based on an idealized model of therapeutic effect but around recovery from toxicity—most commonly that of myelosuppression and specifically neutropenia. By giving myeloid growth factors after standard dose chemotherapy, investigators have demonstrated that several regimens can be delivered every 2 weeks, rather than every 3 weeks. One of the most notable examples of this is CALGB trial 9741 in which women received adjuvant doxorubicin (Adriamycin) and cyclophosphamide (AC) chemotherapy followed by daily filgrastim from days 3-10 of each cycle. After completing the AC chemotherapy, patients received sequential paclitaxel, also on a dose-dense schedule, every 2 weeks with myeloid growth factor support. When compared to every-3-week administration without growth factor support, patients had better disease-free and overall survival without increased toxicity. Dr. Burstein reviews these results along with additional data from Dana-Farber Cancer Institute, where a single injection of the long-acting myeloid growth factor pegfilgrastim (Neulasta) was substituted for daily filgrastim in a phase II trial. In the hands of the Dana-Farber investigators, when pegfilgrastim was incorporated into the dose-dense regimen of AC followed by paclitaxel, the rates of grade 4 neutropenia, febrile neutropenia, and cycle delays were comparable to the results of daily administration of filgrastim from the CALGB trial.

Chemotherapy Dose Delivery
In a provocative article, Dr. Lyman addresses the issues around chemotherapy dose delivery as a quality metric for cancer care. As a leader in health outcomes assessment, Dr. Lyman's research has focused particularly on the risk and consequences of chemotherapy-induced severe and febrile neutropenia. However, here he also focuses on the importance of chemotherapy dose intensity. This is not dose density or increasing dose intensity over that of standard treatment, but rather delivery of full standard doses of chemotherapy to achieve the best therapeutic outcome. In the oft-quoted retrospective data of Bonadonna, when women with breast cancer received < 85% of the planned full dose intensity of adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil [5-FU]) chemotherapy, there was no benefit in terms of survival compared to those patients who received no chemotherapy at all. These data are supported by prospective data demonstrating the impact of delivering full-dose intensity chemotherapy with CAF (cyclophosphamide, doxorubicin [Adriamycin], 5-FU) chemotherapy for women with breast cancer on CALGB 8541. While there are also examples in the lymphoma setting demonstrating the importance of dose, in truth we are not absolutely sure at what level of dose reduction treatment efficacy is compromised, and whether this is the case only in adjuvant and curative settings or whether the importance of dose also applies to palliative approaches.

Addressing these issues is complicated, requiring controlled trials with large sample sizes. What is clear from Dr. Lyman's research is that the frequency of both planned and unplanned reductions in chemotherapy dose intensity remain very common, even in the settings of early stage breast cancer and lymphoma where the evidence base is strongest for support of full-dose chemotherapy. While reasons for these dose reductions are likely multifactorial, they often relate to the physician's concern about toxicities and risk of the treatment to the patient. Clearly prospective data collection is needed to better define where full dose treatment with proactive supportive care measures can improve the safety of the regimen and maintain the therapeutic benefit. Dr. Lyman has nicely addressed the importance for all of us in the cancer field to address the impact of chemotherapy dose delivery both on toxicity and patient benefit as a quality cancer care initiative.

Growth Factor Support and the Older Cancer Patient
One of the ways that we will improve outcomes for our patients in the future is through personalized cancer treatment. This will include an increasingly sophisticated analysis of individual patients' tumor biology through genomics and other biomarkers to develop the best therapeutic strategy with chemotherapy, target agents, or in some cases, local therapy only when the tumor biology is favorable. Accompanying the study of tumor biology, it will be equally important to study the physiology of the patient. Through the work of Dr. Balducci and colleagues, we have become increasingly aware of the importance of the older cancer patient as a special population. But with increasing sophistication, we will be able to look beyond age per se to a more functional assessment of risk for toxicity.
In Dr. Balducci's article, he nicely outlines the large body of evidence supporting the benefit of chemotherapy for most cancers in older individuals, who are selected based on life expectancy and functional reserve. However, even in these "healthy elderly" there is an increased risk of chemotherapy-induced neutropenia that may result. This includes neutropenic infections specifically in the older patient with non-Hodgkin's lymphoma receiving CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) or CHOP-like regimens. In the majority of these clinical trial patients, the rate of neutropenic fever exceeded the NCCN/EORTC/ASCO guidelines of 20%. Therefore, all older lymphoma patients receiving these regimens should be considered for routine first-cycle use of myeloid growth factor support. This is of interest since this same CHOP regimen in the younger patient may have an intermediate risk (10% to 20%) based on the chemotherapy regimen alone.

Clearly analyses of other chemotherapy regimens are needed to compare the risk of neutropenic complications in younger and older cancer patients. In the meantime, Dr. Balducci would suggest that we strongly consider the risk factor of age in consideration of first-cycle prophylaxis of patients receiving myelosuppressive chemotherapy in this intermediate risk range. Hopefully the work of Dr. Lyman and his colleagues will lead to an individual patient risk assessment tool that will refine this decision-making process in the future.

Conclusions
In total, these four articles nicely summarize the current state-of-the-art of our knowledge regarding the complex interplay between chemotherapy dose delivery and myelotoxicity and its impact on short and long term treatment outcomes for our patients. I am thankful to the authors of these articles, for their contributions and for helping chart the course for further investigation.

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References:


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