First-Cycle CSF Use in Breast Cancer and NHL: Guidelines and Recommendations

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Grade 3 and 4 neutropenia as well as febrile neutropenia have been demonstrated to occur in all tumor types and are clearly associated with major morbidity and significant mortality; this is particularly true when myelosuppressive regimens are used with curative intent as is the case in most breast cancer and non-Hodgkin's lymphoma regimens. Myeloid colony-stimulating factors (CSFs) substantially decrease the risk of severe and febrile neutropenia. Although the white cell growth factors might not be cost-effective at lower risks of febrile neutropenia, they clearly benefit other outcomes such as the incidence of severe neutropenia and febrile neutropenia, hospitalization, and mortality. Updated guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the European Organisation for Research and Treatment of Cancer now recommend primary prophylaxis or first-cycle use of white cell growth factors with regimens where the occurrence of febrile neutropenia is approximately 20% (as well as when other risk factors are present). This article briefly describes the rationale for the development of several of the guideline changes as well as highlights some of the ongoing issues related to the use of CSFs.

The utilization of white-cell hematopoietic colony-stimulating factors (CSFs) in the treatment of cancer chemotherapy has undergone an evolution since their first introduction in 1991. When the CSFs were originally introduced, the American Society of Clinical Oncology (ASCO) published a set of guidelines regarding their recommended appropriate use in myelosuppressive regimens that were of moderate to severe intensity and produced at least a 40% incidence of febrile neutropenia. These recommendations were based upon the fact that CSFs were known to be very safe in their administration, were effective in eliminating febrile neutropenia by secondary prophylaxis (meaning following a first episode of febrile neutropenia), and yet were relatively expensive adjuncts to chemotherapy administration.

The 1994 ASCO guidelines,[1] including biannual updates since that time, maintained similar restrictions based on recommendations for patients to receive secondary prophylaxis following an episode of febrile neutropenia in what were considered "curable" malignancies—primarily breast cancer and non-Hodgkin's lymphoma. From their initial publication in 1994, risk factors such as age and prior history of chemotherapy were also acknowledged by the guidelines as a basis for consideration of use of the CSFs.[1,2]

As more data in clinical trials have accumulated, and as newer regimens have been developed in breast cancer and non-Hodgkin's lymphoma (as well as certain other solid tumors for which adjuvant regimens have been shown to be beneficial), the ASCO guidelines have evolved. In addition, the National Comprehensive Cancer Network (NCCN) guidelines published in 2005 and the European Organisation for Research and Treatment of Cancer (EORTC) guidelines also published in 2006 now have recommendations that are entirely consistent with ASCO's updated recommendations. This article briefly describes the rationale for the development of several of the guideline changes as well as highlights some of the ongoing issues related to the use of CSFs.

Chemotherapy-Induced and Febrile Neutropenia

The risk of chemotherapy-induced neutropenia (absolute neutrophil count [ANC] < 500) and febrile neutropenia (defined as an ANC < 500 and a temperature of &ge 38.2°) has significant consequences both for individual patients and subsets of patients given myelosuppressive regimens, particularly with the presence of risk factors that are described subsequently in this article. The risk of chemotherapy-induced neutropenia is known to increase the incidence of hospitalization, the overall costs of therapy for patients, and the incidence of life-threatening infections and even the mortality of patients on certain myelosuppressive regimens.[3] In addition, it can create suboptimal chemotherapy dosing and may be a leading cause of dose reductions, potentially impacting relapse-free and overall survival in breast and non-Hodgkin's lymphoma.[4] Thirdly, chemotherapy-induced neutropenia may have effects on quality of life.[5]
Often, the incidence of severe neutropenia is not appreciated. Very frequently patients will develop severe neutropenia with an ANC < 500 in the interval between chemotherapy doses but the nadir duration is short enough that febrile neutropenia does not occur. An example of the fact that grade 3/4 hematologic toxicities are often underreported has been provided by Dale et al and Lyman et al for a wide variety of randomized clinical trials in non-Hodgkin's lymphoma. [6,7] Overall the incidence of grade 3/4 hematologic toxicity varied from a low of approximately 30% to as many as 70% to 80% of patients with certain regimens. Although these data were reported for non-Hodgkin's lymphoma, similar data exist for breast cancer (in which 48% of patients have severe neutropenic events) and other solid tumors such as ovarian, lung, and colon cancer—all of these malignancies are now treated with moderate to severe myelosuppressive regimens with curative intent, at least for earlier-stage patients. [8-10]

The primary basis for febrile neutropenia in these patients is related to the duration of severe neutropenia (ANC < 500). There is a linear correlation between the incidence of febrile neutropenia and the duration of the neutrophil nadir with roughly 4 to 5 days being the cutoff point where 40% to 50% of patients will develop febrile neutropenia. [11,12] It is this extended nadir that is the target of the CSFs. Although the absolute depth of the nadir is changed very little by prophylaxis with a white cell growth factor, the duration is abbreviated and results in a reduction of febrile neutropenia in the vast majority of published clinical trials by approximately 50%. [12-14]

When Are Growth Factors Most Beneficial?
Myelosuppressive chemotherapy regimens in breast cancer and non-Hodgkin's lymphoma are almost always given in cycles of anywhere from 2- to 4-week intervals. The question must then be asked as to when the white cell growth factors are most beneficial in these regimens. There was an initial bias that there was a cumulative effect of myelosuppressive chemotherapy, with patients receiving multiple cycles being at greatest risk for the development of febrile neutropenia and therefore experiencing the greatest benefit from prophylaxis with a CSF. This is also the rationale for secondary prophylaxis in which one episode of febrile neutropenia is considered to be an acceptable toxicity that can then be eliminated with subsequent use of a CSF in the remaining cycles of chemotherapy. [15]

The rationale for this secondary prophylaxis approach also has a cost-benefit component in which less use of CSFs is required for the latter cycles of chemotherapy administration than would be required to commence CSF therapy with the first chemotherapy cycle. When the actual incidence of febrile neutropenia is examined based on the cycle of chemotherapy, however, the data demonstrate that most febrile neutropenic episodes tend to occur in the first cycle of chemotherapy. This is clearly seen in an article by Lyman et al where the hazard ratio for cycle number 1 of chemotherapy is nearly 2.5 compared to less than 0.5 for all subsequent febrile neutropenic episodes. [7]

One possible explanation for most of the febrile neutropenic events occurring in the first cycle of chemotherapy administration has to do with the fact that the bone marrow in these patients is "naive" and not as responsive to the chemotherapy insult. Hematopoietic progenitors are induced by the chemotherapy insult and in subsequent cycles may be capable of more rapid expansion and differentiation than following the first dose of chemotherapy. Other reasons for subsequent improvement in febrile neutropenic events have to do with dose reduction, dose delays, and the institution of hematopoietic growth factors following a first episode. Nonetheless, it is clear that patients with a wide variety of tumors and regimens are at very high risk of febrile neutropenia beginning with the first-cycle administration of chemotherapy. [7,15]

Cost-Benefit Rationales
The overall cost of an episode of febrile neutropenia can be significant. It was the cumulative cost of febrile neutropenic events in myelosuppressive regimens with at least a 40% incidence of febrile neutropenia that led the ASCO guideline committee to recommend the use white cell growth factors in the first and subsequent cycles with these regimens. This is because the cost of treating 100 patients with the white cell growth factor was outweighed by the cost of hospitalization of the 40 patients who would develop febrile neutropenia if not treated with CSF prophylaxis. In a review of more than 55,000 hospitalizations for febrile neutropenia from 1995 to 2000, Kuderer et al demonstrated that the mean length of stay for these hospitalizations was approximately 11 days and that the mean cost for the hospital stay was $19,000. [16] If patients had no complications the mean cost was a little less at $18,000, but with one or more complications this rose to as much as $37,000. Thus, a single episode of febrile neutropenia is expensive but the overall cost of CSF use for regimens that produce less than 40% incidence of febrile neutropenia remains greater if all patients are treated from the first cycle with a white cell growth factor than if secondary prophylaxis
is used as a strategy.

Other Rationales for First-Cycle CSF Use

Entirely different rationales than cost-benefit are therefore required to justify first-cycle CSF use in breast cancer and non-Hodgkin's lymphoma for which standard chemotherapy regimens produce 30% or even 20% rates of febrile neutropenia. The first of these rationales has to do with maintenance of chemotherapy dose intensity in curable malignancies. A positive relationship has been repeatedly demonstrated between dose intensity and survival in adjuvant or initial therapy for many common tumors including breast, lymphoma, lung, colon, and ovarian cancer. In patients with these tumors achieving improved clinical outcomes may depend on delivering chemotherapy above a certain threshold of dose intensity. One frequently cited report by Bonadonna et al demonstrates that in a 20-year retrospective of breast cancer patients receiving adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil [5-FU]) chemotherapy, those patients that received at least 85% of the planned dose intensity achieved the best relapse-free and overall survival.[4] Patients receiving less than 85% were not statistically benefited in either relapse-free or overall survival as compared to untreated control patients. Similar data of a more recent nature have been described by Budman and colleagues in a Cancer and Leukemia Group B trial[17] and a recent report by Bonnetterre et al showed that chemotherapy dose intensity in a French adjuvant trial of FEC (5-FU, epirubicin, cyclophosphamide) 100 vs FEC 50 mg/m² yielded survival data at 10 years that was statistically better both for disease-free and overall survival in patients receiving FEC 100.[18] Thus a good rationale exists for use of CSFs from cycle number 1 in patients receiving adjuvant or initial therapy for potentially curable malignancies such as non-Hodgkin's lymphoma and early-stage breast cancer in order to optimize chemotherapy dose intensity.

Related to this rationale is the tendency to reduce dose, particularly in older patients. Although "elderly" patients are defined differently in different trials and guidelines, most authors agree that patients 65 and older with breast cancer and non-Hodgkin's lymphoma are often dose-reduced to their detriment.[19,20] These data have also been reported by Lyman et al and demonstrate that patients 60 years of age or older among more than 4,500 non-Hodgkin's lymphoma patients have a higher likelihood of dose reduction than do patients under 60 or even for the entire cohort.[21] Nonetheless, these patients are just as likely to benefit from full dose on time chemotherapy administration with a potentially curable malignancy as are younger patients. Although patients over 65 more frequently develop febrile neutropenia and require hospitalization, they nonetheless do respond to exogenous administration of hematopoietic CSFs and will come very close to equivalence in their tolerability of chemotherapy when given these growth factors starting in the first cycle.[22,23]

A second important rationale for first-cycle use of CSFs has to do with the fact that febrile neutropenia is not solely an economic and inconvenient event, but may in fact be life-threatening. Hospital mortality among a cohort of more than 41,000 patients examined from 1995 to 2000 for a diagnosis of febrile neutropenia demonstrated that there was a 9% to 10% incidence of mortality in non-Hodgkin's lymphoma and in a number of solid tumors as a result of admission for febrile neutropenia.[16] Despite the fact that we are very good at diagnosing febrile neutropenia and providing supportive care, once febrile neutropenia has developed patients remain at risk for death, particularly with the existence of comorbidities and other risk factors.

Efficacy of Myeloid Growth Factors

The original approval of the CSFs for myelosuppressive chemotherapy was based on trials in which the regimens had a febrile neutropenia rate in the placebo arm of approximately 60%.[12,24] In these studies the overall reduction in the incidence of febrile neutropenia with the addition of a granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) was approximately 50%. This was demonstrated in small-cell lung carcinoma with chemotherapy consisting of cyclophosphamide, doxorubicin, and etoposide, which yielded from 50% to 77% placebo rates of febrile neutropenia.[12] More recently, in breast cancer patients treated with doxorubicin and docetaxel (Taxotere), the febrile neutropenia rate in the absence of growth factor was shown to be approximately 38%.[25] When this regimen was selected in the registration trials of pegfilgrastim (Neulasta), the long-acting version of G-CSF, and patients were randomized to either G-CSF or pegfilgrastim, G-CSF again reduced the febrile neutropenic rate by 50%.[13,26] There was some suggestion that pegfilgrastim further reduced this rate, but the studies were not powered to demonstrate a difference between the G-CSF control arm and the pegfilgrastim arm.

These studies tended to validate the ASCO guideline selection of the 40% cutoff for febrile neutropenia as the appropriate lower threshold for institution of primary prophylaxis with a white cell...
growth factor. However, in early 2005, Vogel and colleagues[14] published results in patients with breast cancer receiving single-agent docetaxel. In this study, patients on the placebo arm without growth factor were found to have only 17% febrile neutropenia. Nonetheless, with first-cycle and subsequent use of pegfilgrastim the incidence of febrile neutropenia fell to 1% as did neutropenic hospitalizations. Clearly there was a major clinical benefit with first-cycle use of pegfilgrastim in these patients, although from an economic standpoint the overall cost for the utilization of the white cell growth factor exceeded the projected costs for patients on this regimen who were hospitalized with febrile neutropenia. Another result of the study was the demonstration that 67% of the febrile neutropenic events in the placebo group were shown to occur in cycle number 1 whereas with first-cycle use of pegfilgrastim febrile neutropenia occurred at less than 1%. Regimens with even lower rates of febrile neutropenia also benefit from the use of a CSF. In a study reported by Papeldo et al[27] with a regimen consisting of adjuvant epirubicin (Ellence) and cyclophosphamide with or without lonidamine, febrile neutropenia occurred in the placebo arm at 7% and dropped to 1% with the use of G-CSF—a clinically and statistically significant benefit, although not an economically cost-beneficial one. When the universe of trials comparing placebo and hematopoietic CSFs were compared in a meta-analysis performed by Kuderer et al,[28] the benefit in favor of CSF for the prevention of febrile neutropenia is seen across all studies; the relative risk overall is 0.54 in favor of CSF. Thus, with very few exceptions, a reduction in the incidence of febrile neutropenia with the use of first-cycle CSF appears to be in the 50% range. This same meta-analysis also examined infection-related mortality and found the relative risk in favor of growth factor to be very similar at 0.55.

NCCN/ASCO/EORTC Guidelines: Who Should Receive Growth Factors?

Thus the evolving data on the use of white cell CSFs confirm that first-cycle use reduces febrile neutropenia rates in regimens that yield 40%, 20%, and even 10% incidences of febrile neutropenia. It was based primarily on the Vogel data[14] that the NCCN published its 2005 myeloid growth factor guidelines. Since that time EORTC also published their new guidelines and ASCO updated theirs as well. In each of the guidelines, the risk of a neutropenic event is considered moderate to high when the febrile neutropenic rate is approximately 20%. The American Society of Clinical Oncology recommends use in the range of 20%,[29] the NCCN suggests use when the range is greater than 20%,[30] and the EORTC suggests use when the range is greater than or equal to 20%.[31] Intermediate-risk febrile neutropenia rates are considered to be less than 20% for ASCO with the presence of risk factors and 10% to 20% for the other two guidelines. The NCCN and EORTC do not recommend use when the risk is less than 10%, whereas the ASCO guidelines do not specify a lower threshold but focus more emphasis on the risk factors described below. Regimens that therefore are recommended for primary prophylaxis with a CSF include the majority of those used in non-Hodgkin's lymphoma and in breast cancer with the possible exception of CMF, which has a range of febrile neutropenia below 5%. Data are available within the body of the ASCO guideline describing what expected febrile neutropenia rates might be for given regimens. Increasing emphasis is now being placed upon the associated factors that place patients at high risk for development of febrile neutropenia. The ultimate goal would be to be able to describe precise risk factors in any individual patient and thus be able to predict that a given patient will have a greater than not likelihood of developing febrile neutropenia. According to the NCCN guideline, these risk factors can be broken down into patient-related, treatment-related, tumor-related, and comorbidity categories.[30] Examples of patient-related risk factors include age greater than 65, poor performance status, poor nutritional status, or poor immune function. Comorbidities might include chronic obstructive pulmonary disease, cardiovascular or liver disease, diabetes, or active infection. Tumor-related risk factors include bone marrow involvement with tumor, extensive cancer indicated by high lactate dehydrogenase or low albumin, or the presence of certain tumors such as leukemia, lymphoma, or lung cancer. Finally, treatment-related risk factors are a history of severe neutropenia with similar chemotherapy, intent to give full dose on time chemotherapy with curative intent in breast or lymphoma patients, and concurrent or prior radiation to marrow containing areas. The actual incidence of febrile neutropenia in a given patient is determined by the cumulative probability of a number of risk factors.[2] The presence of zero or one risk factor allows the patient only a small increase in the probability of developing febrile neutropenia whereas the presence of four, five, or six of these risk factors provides a major increase and virtually guarantees that that patient will suffer an event. Thus assessing the patient carefully prior to initiating chemotherapy and applying primary prophylaxis in patients with greater risk is likely to provide the greatest clinical
benefit and the most cost-effective use of CSFs.

Controversies Regarding CSF Use
There remain several issues that are frequently debated regarding the use of white cell growth factors, particularly in breast and lymphoma patients who are being treated with an intent to cure. The first of these relates to whether oral antibiotic prophylaxis is as effective as a CSF in reducing the febrile neutropenia rate (aside from the issue of inducing greater rates of antibiotic resistance). Oral quinolones have been demonstrated in trials in both the United States and Europe to limit the incidence of febrile neutropenia in patients receiving chemotherapy. However, oral antibiotics do not appear to substitute for the use of a white cell growth factor.

This has been demonstrated in trials in which there appears to be an additive affect of oral antibiotics plus CSF[32] and is best demonstrated at least in abstract form from a trial done by Von Minckwitz et al.[33] In this study breast cancer patients were treated with the TAC regimen (paclitaxel [Taxol], doxorubicin [Adriamycin], cyclophosphamide) and then randomized to G-CSF, ciprofloxacin, pegfilgrastim, or pegfilgrastim plus ciprofloxacin. The results demonstrated that ciprofloxacin was less effective than G-CSF or pegfilgrastim in reducing the incidence of neutropenia. The second area of controversy has been whether or not it is safe to administer a CSF on the same day as chemotherapy administration rather than waiting 24 hours. Several studies have been done in relatively small numbers of patients. In breast cancer patients being treated with TAC chemotherapy, Kaufman et al demonstrated that the febrile neutropenia rate was 33% with same day pegfilgrastim vs 11% in those for whom a 24-hour delay was followed.[34] Similarly, Saven et al showed that the febrile neutropenia rate with non-Hodgkin's lymphoma patients was 11% with same day dosing vs 3% in patients receiving their CSF 24 hours later.[35] It is unclear why these differences may exist; however, it may be that the chemotherapy effect on myeloid progenitors in which the chemotherapy is given concomitantly with the CSF results in the death or delay in recovery of those progenitors.

In an effort to reduce the use of CSFs and therefore provide cost benefits, several studies have examined the possibility of reducing the recommended 10 days of administration following chemotherapy. Some good examples of studies in which this question has been addressed are those of Pfreundshuh et al.[36,37] In these studies 10 days of G-CSF administered on days 4 to 13 of a dose-dense CHOP (cyclophosphamide, doxorubicin HCI, vincristine [Oncovin], prednisone) or R-CHOP (CHOP plus rituximab [Rituxan]) regimen in non-Hodgkin's lymphoma was more effective than 7 days of G-CSF. In addition there was a higher infection rate in the 10-day arm as opposed to the 7-day arm.

Pegfilgrastim has an 80-hour serum half-life and is the equivalent of 10 days of G-CSF administration. It appears to be ideal for use in dose-dense 14-day regimens. A publication by Burstein et al in the Journal of Clinical Oncology[38] demonstrated a febrile neutropenia rate of only 1.5% in women with stage I to III breast cancer receiving dose-dense AC (doxorubicin [Adrimycin], cyclophosphamide) followed by paclitaxel as adjuvant or neoadjuvant therapy. An added benefit was the demonstration that there were treatment delays in less than 5% of all cycles and that chemotherapy dose on time exceeded 85% in this study.

Possible Toxicities
Finally, two other theoretical toxicities have been proposed as a result of administration of a CSF. One is the possibility that the CSFs themselves might be tumorigenic. There are data from the Children's Oncology Group study in pediatric acute lymphoblastic leukemia (ALL) patients who were randomized to either G-CSF or placebo that demonstrated that a slightly higher incidence of secondary acute myelogenous leukemia occurred in those patients receiving G-CSF.[39] These data have not been confirmed in other trials, but if they are, they may be a result of the relative instability of the malignant clone in pediatric ALL and the possibility that G-CSF, for which there are receptors on the leukemic blasts, is driving a secondary cytogenetic event.

The second concern has to do with the possibility that there is lineage steal in patients receiving a white cell growth factor with the development of anemia. A slightly higher incidence of anemia has been demonstrated in 14-day regimens in breast cancer and lineage steal has been postulated as the etiology.[40] However, a more likely explanation is that anemia in these patients is due to nutritional deficiency or delayed recovery of red cell precursors, both of which can be easily addressed with the use of erythropoietin and parenteral iron.

Conclusions
In summary, grade 3 and 4 neutropenia as well as febrile neutropenia have been demonstrated to occur in all tumor types and are clearly associated with major morbidity and significant mortality; this is particularly true when myelosuppressive regimens are used with curative intent as is the case...
in most breast cancer and non-Hodgkin's lymphoma regimens. Myeloid CSFs substantially decrease the risk of severe and febrile neutropenia and do so consistently whether that risk is 20%, 40%, or 60%. Although the white cell growth factors might not be cost-effective at lower risks of febrile neutropenia, they clearly benefit other outcomes such as the incidence of severe neutropenia and febrile neutropenia, hospitalization, and mortality.

Guidelines now recommend primary prophylaxis or first-cycle use of white cell growth factors when the incidence of febrile neutropenia is 20% or more and particularly when there are added risk factors or in elderly patients. Treatment with hematopoietic CSFs should begin 1 to 3 days following chemotherapy and continue for an equivalent of 7 to 10 days with standard dose regimens and 10 days with dose-dense regimens in order to effectively continue through the nadir of neutrophil counts.

Disclosures:
The authors 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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