A Way Forward on the Medically Appropriate Use of White Cell Growth Factors

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Are Hematopoietic Colony-Stimulating Factors Over- or Underused?

Since their introduction, there has been debate about the benefits, risks, and costs of hematopoietic colony-stimulating factors (CSFs). We suggest that the use of CSFs to allow dose maintenance of chemotherapy for common metastatic solid tumors is unsupported by evidence, and we should reconsider using a \$3,500-per-cycle injection for a supportive care drug without major benefit.¹

Recent studies have documented concerns about appropriate CSF use. Potosky et al² prospectively identified 1,849 patients with lung or colorectal cancer who received palliative chemotherapy from 2003 to 2005. Only 17% of high-risk patients received appropriate primary prophylaxis. CSFs were used to maintain dose-intensity in 257 patients, of whom 18% were at intermediate risk (10% to 20% risk) and 10% were at low risk (< 10% risk) of febrile neutropenia (FN). Compared with American Society of Clinical Oncology (ASCO) guidelines³ (Table 1), 96% of CSF use can be judged not appropriate.

Two reports from Ramsey et al^{8,9} are relevant. The first found that in 2,728 patients with cancer at low risk of FN, 10% of those with breast, 7% of those with colorectal, and 21% of those with non-small-cell lung cancers received CSFs. Most use did not conform to product labeling or practice guidelines.⁸ The second linked Puget Sound Cancer Registry data with insurance claims from four payers representing 75% of those insured from 2002 to 2005 and found no evidence that CSF as primary prophylaxis was associated with a reduction in antibiotic use or inpatient or outpatient visits in breast, colorectal, or non-small-cell lung cancer.⁹

Kuderer et al¹⁰ rebutted that CSFs were perhaps underused. They argue that “initiation of the CSFs early in the first cycle of chemotherapy and continuation through all cycles of a chemotherapy regimen (primary prophylaxis) has been shown to substantially reduce the risk of FN as well as infection-related and early all-cause mortality, while decreasing the need for chemotherapy dose reductions and delays,”^{10(p911)} without referring to any specific cancer types.

How Can These Disparate Conclusions Be Reconciled?

CSFs are essential if dose-dense treatment is definitively beneficial. Dose-dense chemotherapy (every 2 v every 3 weeks) requires supportive CSFs, and when used as adjuvant treatment of breast cancer, it has improved overall (hazard ratio, 0.84; 95% CI, 0.72 to 0.98) and disease-free survival in estrogen receptor (ER) –negative patients^{11,12} but has had no advantage over conventional-dose therapy

for ER-positive patients.¹³ Dose-dense therapy has been rapidly and widely adopted as standard therapy. A recent estimate found Medicare spent at least \$40 million in 2005 for CSFs in support of dose-dense therapy in ER-positive women without any disease benefit.¹⁴ Febrile events occurred in 15% to 20% of the women, higher than in the Medicare-age subset of the INT (Intergroup) 9741 trial, suggesting that this therapy may not be as well tolerated in older women,¹⁵ and only 1% to 4% lower if CSFs were used.

The benefit of prophylactic CSFs in reducing the risk of FN and infection and allowing higher dose-intensity for treating lymphomas was assessed in two meta-analyses^{16,17} and a recent trial of 1,080 patients.¹⁸ Each report found that CSFs did not change response rate, progression-free survival, overall survival, or quality of life compared with treatment without primary prophylaxis. Regardless, CSFs have become an integral part of lymphoma treatment, because the regimens have a high rate of FN.

CSFs for Dose Maintenance in Routine Noncurative Cancer Care

To the best of our knowledge, there is no randomized trial evidence regarding treatment of the most common metastatic cancers that demonstrates compromised treatment outcome when dose is reduced by protocol or that indicates better medical outcomes result from dose maintenance supported by CSFs. Specifically, there are no studies in breast, colorectal, or hormone-refractory prostate cancer; there are negative studies in non-small-lung cancer^{19–24}; and no benefit has been demonstrated from dose-intensification²⁵ or maintenance^{26–28} in small-cell lung cancer. Even in small-cell lung cancer treatment, primary prophylaxis is not recommended.²⁹

Lyman et al³⁰ reviewed 25 randomized trials comprising more than 6,000 patients who did or did not receive primary CSF prophylaxis. The reduction in overall mortality (relative risk, 0.87; 95% CI, 0.82 to 0.92; $P < .001$) was confined to patients treated with deliberately dose-intensified regimens, not recommended outside a clinical trial because of the inconsistent primary anticancer survival benefit. In 11 trials, using CSFs to maintain conventional dose, rate, and schedule did not change mortality (relative risk, 0.94; 95% CI, 0.88 to 1.01; $P = .088$).

CSFs Used to Treat FN or Afebrile Neutropenia

In the CanCORS (Cancer Care Outcomes Research and Surveillance) study,² the likelihood of receiving a CSF was increased if FN was documented; 22% of patients received CSFs if they had FN (adjusted

Table 1. Comparison of Major Guidelines

Use	ASCO 2006	NCCN 2011	EORTC 2011
Curative intent, such as dose-dense treatment			
Primary prophylaxis			
High risk	“Primary prophylaxis is recommended for the prevention of FN in patients who are at high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen.”^{4(p3188)} For dose-dense regimens, CSFs are required and recommended.	High-risk patients (risk > 20%): “Prophylactic treatment is recommended for any patient considered at high risk, regardless of whether the treatment is intended to be curative, to prolong survival or to manage symptoms.”^{5(p4)}	“In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as a supportive treatment.”^{6(p19)} Recommendation grade: A “If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment or when the treatment intent is to prolong survival.”^{6(p19)} Recommendation grade: A
Intermediate risk		“In all three categories of treatment intent, the panel recommends individualized consideration of CSF use based on physician-patient discussion of the risk-benefit ratio of the likelihood of developing FN, the potential consequences of a neutropenic event and the implications of reduced chemotherapy dose delivery.”^{5(p4)} When the intent of chemotherapy is to prolong survival or manage symptoms, the use of CSFs is a difficult decision and requires careful discussion between the physician and patient. If patient risk factors determine the risk, CSF use is reasonable. If the risk is from the chemotherapy regimen, other alternatives, such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.	
Low risk		“For low-risk patients, as defined by a < 10% risk, routine use of CSFs is not considered cost-effective and alternative treatment options are appropriate. However, CSFs may be considered if the patient is receiving curative or adjuvant treatment and is at significant risk for serious medical consequences of FN, including death.”^{5(p4)}	
Palliative intent	Does not differentiate	“Prophylactic CSF is recommended for any patient considered at high risk, regardless of whether the treatment is intended to be curative, prolong survival, or manage symptoms.”^{5(p4)} When the intent of chemotherapy is designed to prolong survival or manage symptoms, the use of CSFs is a difficult decision. “Other alternatives, such as the use of less myelosuppressive regimen or dose reduction, if of comparable benefit, should be explored.”^{5(p4)}	“Where treatment intent is palliative, use of less myelosuppressive chemotherapy or dose/schedule modification should be considered.”^{6(p19)} Recommendation grade: B
Secondary prophylaxis	“Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.”^{4(p3191)}		Does not specify
Abbreviations: ASCO, American Society of Clinical Oncology; CSF, colony-stimulating factor; EORTC, European Organisation for Research and Treatment of Cancer; FN, febrile neutropenia; NCCN, National Comprehensive Cancer Network.			

odds ratio, 1.39; 95% CI, 0.88 to 2.20; $P = .16$), compared with 7% if no FN was recorded. Use of CSFs for treatment of FN or febrile neutropenia³¹ is clearly unwarranted. Other recent studies have not addressed this issue.⁸

What Is the Harm in Using CSFs?

There is a history of concern about adjuvant chemotherapy–induced acute leukemia or myelodysplastic syndrome (AML/MDS)^{32,33} Current evidence is reassuring, in that younger patients with breast cancer have shown no increase in AML/MDS with dose-dense treatment.^{11,34} However, in elderly woman, Hershman et al³⁵ reported a hazard rate for AML/MDS after adjuvant breast cancer treatment of 2.1 with CSFs (95% CI, 1.12 to 4.08). There are other less serious adverse effects, the most common being bone pain reported in 10% of controls and 20% of CSF-treated patients, with a relative risk of 4.³⁶

Are CSFs a Prudent Use of Societal Resources?

At our institution, the charge for each 6-mg dose of pegfilgrastim (Neulasta; Amgen, Thousand Oaks, CA) is \$4,800, and Medicare reimbursement is \$2,200. Combined pegfilgrastim and filgrastim (Neupogen; Amgen) sales—before markup at the office—in 2010 were \$4.8 billion, with 75% in the United States.³⁷ Pegfilgrastim accounted for 5.2% of all drug expenditures in Medicare Part B and was the fifth largest single Medicare drug office expense, at a cost of more than \$500 million in 2008.³⁸

Before 2006, a 40% risk of FN constituted the consensus cost and clinical threshold justifying CSFs. The 2006 ASCO CSF guideline update⁴ lowered the FN threshold risk to 20%, if no other equally effective regimen was available. This change reflected an increased awareness of FN hospitalization rate as a potentially important outcome based predominately on a study showing pegfilgrastim reduced FN from 17% to 1% with docetaxel in metastatic breast cancer (without data on response rate, disease-free survival, or overall survival).³⁹

No study has shown that CSFs are cost effective, because there is no evidence that they prolong life or improve quality of life in the treatment of metastatic cancer. Cost analyses have been primarily cost-minimization studies, because CSFs rarely reduce FN mortality. Key factors in addition to the risk of FN include the patterns of care for FN (hospitalization or outpatient), the rate of expensive outliers, and the price of CSFs.

Two manufacturer-sponsored reports have compared primary versus secondary prophylaxis when used in support of adjuvant breast cancer chemotherapy. The first found an acceptable cost-effectiveness ratio if the rate of FN was greater than 38%⁴⁰ (which no current regimens involve), and the other found the CSF strategy cost per avoided FN episode to be \$48,000.⁴¹ There have been no recent studies in metastatic disease.

Why Do Oncologists Prescribe CSFs if There Is Minimal Evidence for Benefit?

There are likely to be multiple reasons. First, these drugs have been promoted heavily. Second, physicians derive substantial income from these drugs, with revenue ranging from 6% (\$141) to 53% (\$1,312) per injection.¹ In the CanCORS report,² health maintenance organization physicians used half as much as those in private practice (odds ratio, 0.44; 95% CI, 0.32 to 0.66). Third, most oncologists are unaware of the potential harm of AML/MDS and/or the lack of benefit in patients with ER-positive breast cancer. Fourth, no one desires FN, and pegfilgrastim is easy to use. Fifth, no one is watching or attempting

to restrain costs. Finally, some physicians worry about malpractice if they do not use CSFs. This is a legitimate worry if CSFs are not used when clearly indicated, such as in dose-dense chemotherapy for breast cancer, but it is unlikely in metastatic cancer, given that all the guidelines agree that dose reduction is an appropriate strategy.

How Did We Arrive at Widespread Use Without Clinical Trial Justification?

To our knowledge, since the approval of CSFs for general oncologic use, there have been no trials designed to confirm whether dose maintenance with CSF is a better strategy than dose reduction in the treatment of patients with metastatic cancer. A majority of studies since US Food and Drug Administration approval have been large postmarketing patterns of care studies documenting the rapid adoption of CSFs and continued attempts to improve cancer treatment results with dose-intensification. In addition, there have been few small, usually underpowered, trials assessing lower, less expensive, doses versus the full dose of CSFs,^{42–45} with mixed results. As a consequence, we still do not have the usual strength of scientific evidence indicating that dose maintenance with CSFs in support of treatment of metastatic disease leads to better outcomes.

The Way Forward to Evidence-Based Use of CSFs

Increased concern about escalating costs^{46–48} should cause us to examine each component of current care. Oncology professional societies have demanded some demonstrable improvement in an important outcome before adoption of a new technology.⁴⁹ The lack of proven benefit from CSFs in support of therapy in common advanced solid tumors, the high cost, the disparate US and world use patterns with no difference in mortality,⁵⁰ and the potential for or appearance of economic self-interest should give the oncology community pause.

There are concrete steps the US oncology community can take to foster more evidence-based care. The Quality Oncology Practice Initiative⁵¹ could add overuse as a quality criterion⁵² and report CSF use in palliative-intent regimens when there is less than a 20% risk of FN. The major guideline groups (European Organisation for Research and Treatment of Cancer,⁶ National Comprehensive Cancer Network,⁵ and ASCO⁴) should endorse dose modification as an equally appropriate and preferred strategy in the absence of proven benefit.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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