Management of Chemotherapy-induced Neutropenia with Colony-stimulating Factors

a report by

Gary H Lyman

Professor of Medicine, Division of Medical Oncology, and Director, Health Services and Outcomes Research, Duke University

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Myelosuppression, including chemotherapy-induced neutropenia and febrile neutropenia, is the major dose-limiting toxicity of cancer chemotherapy. The myeloid colony-stimulating factors have been shown to reduce the risk of febrile neutropenia and its complications. These agents are available globally and are utilised worldwide in oncology practice to support patients receiving cancer therapy. Clinical practice guidelines are available from several international professional organisations.

Chemotherapy-induced Neutropenia

Febrile neutropenia and its complications continue to be associated with substantial morbidity, mortality and cost. Haematological toxicity associated with cancer chemotherapy occurs most frequently during the initial cycles, but varies across patient populations and treatment programmes (see Figure 1). A number of studies have also indicated that chemotherapy-induced neutropenia is associated with improved treatment efficacy, presumably due to the delivered chemotherapy dose intensity. Neutropenic complications frequently result in subsequent reductions in chemotherapy dose intensity, compromising disease-free and overall survival in patients treated with curative intent. Reduced chemotherapy dose intensity appears to be more common among elderly or obese cancer patients and among certain racial and socioeconomic subgroups.

Risk Factors for Chemotherapy-induced Neutropenia and Its Complications

Neutropenic complications including febrile neutropenia, infection-related mortality and dose reductions and delays are more frequent among elderly cancer patients receiving chemotherapy. While the risk of cancer increases considerably among the elderly, increasing age is associated with a reduced marrow reserve and more frequent co-morbid medical conditions accompanied by declines in renal and hepatic function, increasing the risk of treatment-related complications. Other variables that increase the risk of neutropenic complications include the treatment regimen and certain patient characteristics such as functional status and medical co-morbidities. In order to more accurately predict the risk of neutropenic complications, multivariate risk models are undergoing extensive validation and may soon be available to assist clinical decision-making in oncology practice (see Figure 2).

Colony-stimulating Factors

The myeloid growth factors, and most notably granulocyte colony-stimulating factor (G-CSF), have demonstrated the ability to reduce the incidence and severity of neutropenia and febrile neutropenia while improving chemotherapy dose intensity. The long-acting myeloid growth factor pegfilgrastim appears to have several advantages including patient convenience, improved compliance and, potentially, greater potency. Multiple randomised controlled trials (RCTs) have consistently shown the efficacy and safety of G-CSF, which has recently been confirmed in a meta-analysis of RCTs in adult cancer patients receiving cancer chemotherapy. Significant reductions in the risk of febrile neutropenia were observed across studies for both solid tumour patients and those with non-Hodgkin’s lymphoma across adult age groups and all forms of G-CSF. Of note, a significant reduction in the risk of febrile neutropenia was observed across a broad range of baseline levels of risk ranging from 17 to 90%. As shown in Figure 3, the baseline risk of febrile neutropenia in the control arms of these trials ranges across the full spectrum of risk. In fact, a significant inverse relationship between the baseline risk of febrile neutropenia and the relative risk reduction with G-CSF was found (see Figure 3). This analysis also demonstrated a significant reduction in infection-related and early all-cause mortality. These observations are consistent with that of a Cochrane meta-analysis of therapeutic CSF in patients hospitalised with febrile neutropenia following cancer chemotherapy. The meta-analysis also confirmed the ability of these agents to sustain chemotherapy relative dose intensity averaging 95% in G-CSF patients compared with 88% in control study arms. While few studies have been adequately powered to study overall survival or second malignancies, no increase in mortality or risk of second malignancies has been observed in RCTs.

Myeloid Growth Factor Use in the Elderly Cancer Patient

The risk of cancer increases with increasing age. Patients 65 years of age and above account for some 60% of cancer diagnoses and as many as 70% of cancer deaths. Nevertheless, older patients able to tolerate standard chemotherapy regimens and schedules appear to derive nearly as much benefit from systemic chemotherapy as younger cancer patients. However, clearly, increasing age is a risk factor for...
prophylactic myeloid growth factors in older cancer patients have disease outcome.18,33–38 However, older patients appear to be nearly as observed among elderly cancer patients with potentially compromised Supportive Oncology may result in a higher mortality in those hospitalised for febrile haematological toxicity, including neutropenic complications that may result in a higher mortality in those hospitalised for febrile neutropenia.7 Greater reductions in chemotherapy dose intensity are also observed among elderly cancer patients with potentially compromised disease outcome.19,33–38 However, older patients appear to be nearly as responsive to the myeloid growth factors as younger patients.39,40 RCTs of myeloid growth factor use when the risk is less than 10% (see Figure 4). Likewise, prophylactic G-CSF is recommended when dose-dense or dose-intense chemotherapy has been shown to have survival benefit. Finally, where a reduction in chemotherapy dose intensity may be associated with a poor outcome, consideration of G-CSF prophylaxis to maintain dose intensity is recommended.
Table 1: Critical Appraisal of Myeloid Growth Factor Guidelines

<table>
<thead>
<tr>
<th>Category</th>
<th>ASCO 2006 (%)</th>
<th>EORTC (%)</th>
<th>NCCN (%)</th>
</tr>
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<tbody>
<tr>
<td>Scope and purpose</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Stakeholder involvement</td>
<td>42</td>
<td>50</td>
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<tr>
<td>Rigor of development</td>
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<tr>
<td>Clarity and presentation</td>
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<td>83</td>
<td>100</td>
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<tr>
<td>Applicability</td>
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<td>67</td>
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<tr>
<td>Stakeholder involvement</td>
<td>67</td>
<td>67</td>
<td>33</td>
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Modified from Lyman GH, 2007.44

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based on the type of cancer, chemotherapy regimen, patient-specific risk factors and treatment intention, a formal risk assessment is encouraged (see Figure 5). Like the EORTC guidelines, the NCCN guidelines recommend the use of G-CSF prophylaxis in cancer patients at 20% or greater risk of febrile neutropenia. If there are additional risk factors that place the patient at greater risk of febrile neutropenia or serious consequences, those receiving an intermediate-risk regimen in the range of 10–20% may be offered prophylactic G-CSF. The NCCN guidelines also recommend the use of CSFs to sustain or maintain treatment intensity in those with curable cancers.

American Society of Clinical Oncology Guidelines

While the original ASCO guidelines for the CSFs were published in 1994, the updated 2006 ASCO White Blood Cell Growth Factor Guideline also recommends the use of CSF prophylaxis when risk is approximately 20% or greater.44 Likewise, these agents are encouraged when special circumstances such as older age, co-morbid illnesses, previous febrile neutropenia and other risk factors for serious infection place a patient at an increased risk of febrile neutropenia and an equally effective regimen is not available. The principal evidence for the efficacy of the myeloid growth factors considered was based on the results of multiple RCTs and the recent meta-analysis of 17 RCTs of prophylactic G-CSF.28 Derivative products available with the guidelines include executive and patient summaries, a PowerPoint slide set and a worksheet to assist dissemination and application of the guidelines. These have been generated and are available at the ASCO website (www.asco.org).

A comparison of the three guidelines based on a critical appraisal has recently been reported.43 Specific clinical content areas were extracted from each guideline and the comparative quality of the guidelines evaluated. While the NCCN guidelines are more concise and practical, the EORTC and ASCO guidelines were more rigorous. The recommendations from these guidelines are remarkably consistent for both primary and secondary prophylaxis with the CSFs. The guidelines are also similar in recommending consideration of their use in the elderly, sustaining chemotherapy dose intensity and individualised risk assessment based on patient-specific risk factors such as previous febrile neutropenia, prior chemotherapy, advanced stage, age of 65 years or above, poor performance, nutritional status, co-morbidities and low baseline blood counts. The quality of the guidelines is generally very good, with little difference in issues related to the scope and purpose, stakeholder involvement and applicability of the guidelines.43,45 The NCCN guidelines undergo a more explicit and thorough independent and external review. The ASCO and EORTC guidelines state individual panel member conflicts of interest, whereas the NCCN guidelines only reflect general potential panel conflicts. On the other hand, the NCCN guidelines are updated annually and the use of algorithms is helpful for comprehension and application.

Cost and the Use of the Myeloid Growth Factors

The decision of whether to use a CSF in chemotherapy patients should be based primarily on clinical indications guided by the recommendations discussed above. However, the cost of the myeloid growth factors raises economic considerations at the societal level that should be balanced against the reduction in costs of hospitalisation, any reduction in early mortality from infection and the potential effect of chemotherapy dose intensity on patient survival. The cost of hospitalisation for febrile neutropenia varies considerably, ranging from US$10,000 to US$20,000 per episode in most US studies.1,46,47 Economic analyses based on the efficacy demonstrated in RCTs and the trade-off between costs of growth factor use and the reduction in risk or duration of febrile neutropenia have provided estimates of overall treatment costs.46,47

While the results of these studies have not had a direct influence on the recommendations provided by clinical practice guidelines, the
economic analyses have demonstrated that prophylactic myeloid growth factor use may reduce costs in many clinical settings. A recent study has estimated a net cost saving with primary prophylaxis with G-CSF at a threshold risk of febrile neutropenia of 20% or greater based on average US direct medical costs for hospitalisation for febrile neutropenia. The addition of indirect and out-of-pocket costs with febrile neutropenia to the analysis results in greater net cost savings with myeloid growth factors. The use of the myeloid growth factors used at the time of hospitalisation for febrile neutropenia may result in further cost savings by reducing the length of hospitalisation. Recent studies have demonstrated the potential clinical and economic value of targeting the myeloid growth factors towards patients at greatest risk based on accurate and valid predictive models.

Conclusions

Prophylaxis with the colony-stimulating agents represents an effective and reasonably cost-effective method to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy. Guidelines for the use of the myeloid growth factors from major professional organisations support their use when the risk of febrile neutropenia is 20% or greater and in a number of special circumstances, including the elderly or those with serious co-morbidities. While indications for the appropriate use of these agents have expanded, continued monitoring for any safety signals is essential. Efforts to define better strategies for identifying patients who are at an increased risk and are most likely to benefit from myeloid growth factor support are under way.
INTRODUCTION

The European Oncology Nursing Society (EONS) has provided support to cancer nurses across Europe since 1984. The mission of EONS is to add value to the work of its individual members and national societies in delivering care to patients with cancer. It aims to assist in the promotion of healthy communities through influencing, research and education.

The changing landscape of cancer management in relation to cancer treatments, new technologies, psychosocial care and health care provision has meant a significant shift in the way nurses apply their clinical skills and knowledge in the workplace. However, the professional development and status of cancer nurses across Europe is not uniform and EONS strategic agenda (CARE) aims to address this inequality by working with oncology nurses through their national societies.

STRATEGIC PRIORITIES

Communication
Communicating with and to oncology nurses across Europe remains a challenge. Developing diverse communication pathways is complex and EONS is committed to doing this by continuing to produce and distribute (through the national societies) a newsletter four times a year. The EONS website (part of Cancerworld) is an established forum for cancer nurses and EONS will be developing multi-language sections within the site as well as options for interactive forums to promote professional discussion, information and networking. The European Journal of Oncology Nursing continues to be one of the leading cancer journals and celebrated 10 years of publication in 2006.

Political Agenda
EONS is one of the professional cancer societies that form part of the umbrella organisation renamed ECCO in 2007 (European CanCer Organisation) previously known as FECS – Federation of European Cancer Societies. The organisation provides a collective political voice in Europe. EONS is also a member of the European Specialist Nurses Organisation (ESNO) which consists of associations from both European Nursing Specialist and Nursing Interest Groups. The organisation acts as a platform to represent nursing in the wider political forum.

Research
Promoting evidence based clinical practice through research has always been a core function of EONS. Various grants are distributed through EONS to promote and facilitate research initiatives. One of the priorities is to develop a European cancer nursing research network which will enable wider collaboration, participation and sharing of research evidence as well as build a body of research and development expertise.

Education
The themes as priorities in education are to develop cancer nurse educators to develop and accredit teaching programmes which have education quality standards as part of the review process. Inequality in accessing post-registration cancer nursing education exists across Europe. Alongside this work is the commitment to develop specialist education and leadership programmes which can be viewed in www.cancerworld.org/eons

Notwithstanding the busy agenda the patient experience lies at the heart of the CARE Strategy. By utilising and working in collaboration with patients, EONS will continue to provide a unique contribution to the agenda of cancer care in Europe, whilst promoting the unique contribution of cancer nursing in this process.

For more information on EONS, please contact the secretariat at eons.secretariat@skynet.be