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Position Paper

EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours

M.S. Aapro[a,*,m], D.A. Cameron[b,n], R. Pettengell[c,o], J. Bohlius[d,p], J. Crawford[e,q], M. Ellis[f,r], N. Kearney[g,s], G.H. Lyman[h,t], V.C. Tjan-Heijnen[i,u], J. Walewski[j,v], D.C. Weber[k,w], C. Zielinski[l,x], European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party

[a]Multidisciplinary Oncology Institute, Clinique de Genolier, 1, route du Muids, 1272 Genolier, Switzerland
[b]Department of Oncology, University of Edinburgh and Western General Hospital, Edinburgh, Scotland
[c]Department of Haematology, St George's Hospital, University of London, London, UK
[d]Department I of Internal Medicine, University of Cologne, Cologne, Germany
[e]Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, NC, USA
[f]UAE University, Faculty of Medicine and Health Sciences, Abu Dhabi, United Arab Emirates
[g]Cancer Care Research Centre, Department of Nursing and Midwifery, University of Stirling, Stirling, UK
[h]James P Wilmot Cancer Center, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[i]Radboud University Nijmegen, Department of Medical Oncology, Nijmegen, The Netherlands
[j]The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warszawa, Poland
[k]Department of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland
[l]Clinical Division of Oncology, Department of Medicine I, University Hospital, Central European Cooperative Oncology Group, Vienna, Austria

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ABSTRACT

Chemotherapy-induced neutropenia is not only a major risk factor for infection-related morbidity and mortality, but is also a significant dose-limiting toxicity in cancer treatment. Patients developing severe (grade 3/4) or febrile neutropenia (FN) during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy. This may impact on

* *Corresponding author:* Tel.: +41 22 366 9106; fax: +41 22 366 9131.
E-mail address: maapro@genolier.net (M.S. Aapro).
[m] Member of the EORTC Board and Chair of the EORTC Task Force Elderly.
[n] Representative of the EORTC Breast Cancer Group.
[o] Member of the EORTC and Lymphoma Expert.
[p] Methodology Expert.
[q] Member of MASCC (Multinational Association for Supportive Care in Cancer) and US Expert.
[r] Member of the EORTC Infectious Diseases Group.
[s] Nursing Expert, mandated by EONS (European Oncology Nursing Society).
[t] US Expert.
[u] Representative of the EORTC Lung Cancer Group.
[v] Representative of the EORTC Lymphoma Group.
[w] Representative of the EORTC Radiation Therapy Group.
[x] Breast Cancer Expert and Representative of CECOG (Central European Cooperative Oncology Group).

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the success of treatment, particularly when treatment intent is either curative or to prolong survival. The incidence of severe or FN can be reduced by prophylactic treatment with granulocyte-colony stimulating factors (G-CSFs), such as filgrastim, lenograstim or pegfilgrastim. However, the use of G-CSF prophylactic treatment varies widely in clinical practice, both in the timing of therapy and in the patients to whom it is offered. While several academic groups have produced evidence-based clinical practice guidelines in an effort to standardise and optimise the management of FN, there remains a need for generally applicable, European-focused guidelines. To this end, we undertook a systematic literature review and formulated recommendations for the use of G-CSF in adult cancer patients at risk of chemotherapy-induced FN. We recommend that patient-related adverse risk factors such as elderly age (⩾65 years), be evaluated in the overall assessment of FN risk prior to administering each cycle of chemotherapy. In addition, when using a chemotherapy regimen associated with FN in >20% patients, prophylactic G-CSF is recommended. When using a chemotherapy regimen associated with FN in 10–20% patients, particular attention should be given to patient-related risk factors that may increase the overall risk of FN. In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF support is recommended. Similarly, if reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis may be used to maintain chemotherapy. Finally, studies have shown that filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents to prevent FN and FN-related complications, where indicated.

1. Introduction

Chemotherapy-induced febrile neutropenia (FN), is a serious side effect of cancer treatment, commonly occurring during the initial cycles of cytotoxic therapy[1–6] and increasing in frequency with both the depth and duration of neutropenia.[7,8] As well as having an impact on quality of life,[9] chemotherapy-induced FN predisposes patients with cancer to serious and often life-threatening infections.[10,11] Given the seriousness of FN, the majority of patients who develop this complication are admitted to hospital for evaluation and administration of broad-spectrum parenteral antibiotics.[11]

In addition to infections, chemotherapy-induced FN often also results in lengthy treatment delays and dose reductions, which have been shown to compromise treatment.[12–18] The risk of developing FN appears to depend on a variety of factors, including tumour type, chemotherapy regimen and patient-related risk factors.[10,19–21]

Clearly, prevention of chemotherapy-induced FN should be considered a clinical priority. However, there is considerable diversity in the strategies used to reduce the incidence of this complication. Recombinant human granulocyte colony-stimulating factors (G-CSFs) or granulocyte-macrophage colony-stimulating factors (GM-CSFs) are the only agents currently available that can treat or prevent neutropenia and therefore reduce its associated complications.[10,19,22]

The use of antibiotic prophylaxis to prevent infection and infection-related complications in cancer patients at risk of neutropenia,[23,24] remains a matter of debate despite the publication of a large meta-analysis[25] and a systematic review.[26] In these analyses, the provision of prophylactic antibiotics was significantly associated with a reduction in the incidence of FN and of infection-related mortality. The working party and the EORTC Infectious Disease Group strongly suggest that caution be used; general antibiotic prophylaxis could lead to the emergence of resistance, so it is essential that a balance is achieved between potential harms and benefits to patients.[27]

In Europe, prophylactic administration of G-CSF (filgrastim and lenograstim) or the more recently introduced pegylated form of G-CSF (pegfilgrastim), which has a longer duration of action,[28–31] is generally used to treat at-risk patients. However, the criteria for determining patients who are at risk of developing FN or prolonged neutropenia has not been clearly defined. Patients who have experienced a neutropenic complication in a previous cycle of chemotherapy, may receive G-CSF to avoid another neutropenic event. Alternatively, chemotherapy may be delayed or doses reduced in subsequent cycles of treatment without administration of G-CSF. Chemotherapy delays or reductions resulting from an episode of FN may have detrimental clinical consequences, as they lead to a decrease in the chemotherapy dose delivered during a certain time period.[32] In addition, G-CSF is sometimes used therapeutically in order to reduce the severity and duration of ongoing neutropenia.[33,34]

Increasingly, G-CSF is being used prophylactically to support dose-dense and dose-intense chemotherapy regimens. Several examples suggest that dose-dense chemotherapy is associated with survival benefits over standard regimens.[35–39] In fact, the dose-dense and -intense regimen R-CHOP-14 is considered by many to be the new standard in non-Hodgkin's lymphoma (NHL) treatment. The superior survival benefits of this regimen compared to CHOP-14 have been suggested by two recent phase III trials.[40,41]

Given the wide diversity in G-CSF use, it is perhaps unsurprising that recommendations from current clinical