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Position Paper

2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours

M.S. Aapro [a,*,m], J. Bohlius [b,n], D.A. Cameron [c,o], Lissandra Dal Lago [d,p], J. Peter Donnelly [e,q], N. Kearney [f,r], G.H. Lyman [g,s], R. Pettengell [h,t], V.C. Tjan-Heijnen [i,u], J. Walewski [j,v], Damien C. Weber [k,w], C. Zielinski [l,x]

[a] Multidisciplinary Oncology Institute, Clinique de Genolier, 1, route du Muids, 1272 Genolier, Switzerland
[b] Institute of Social and Preventive Medicine, University of Bern, Switzerland
[c] Department of Oncology, University of Edinburgh, Edinburgh, Scotland, UK
[d] EORTC Headquarters, Av. E. Mounier 83, 1200 Brussels, Belgium
[e] Radboud University Nijmegen, Department of Medical Oncology, Nijmegen, The Netherlands
[f] School of Nursing and Midwifery, University of Dundee, 11 Airlie Place, Dundee, Scotland, UK
[g] Duke University and Duke Comprehensive Cancer Center, Durham, NC, USA
[h] Department of Haematology, St George's Hospital, University of London, London, UK
[i] Maastricht University Medical Centre, Maastricht, The Netherlands
[j] The Maria Sklodowska-Curie Memorial Cancer Institute and Oncology Centre, Warszawa, Poland
[k] Radiation Oncology, Geneva University Hospital, Geneva, Switzerland
[l] Clinical Division of Oncology, Department of Medicine I, Medical University Vienna, Austria

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ABSTRACT

Chemotherapy-induced neutropenia is a major risk factor for infection-related morbidity and mortality and 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 the success of treatment, particularly when treatment intent is either curative or to prolong survival.

* *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 Task Force Elderly.
[n] Methodology Expert.
[o] Representative of the EORTC Breast Cancer Group.
[p] Representative of the EORTC Headquarters.
[q] Representative of the EORTC Infectious Disease Group.
[r] Nursing Expert, mandated by EONS (European Oncology Nursing Society).
[s] US Expert.
[t] Member of the EORTC and Lymphoma Expert.
[u] Representative of the EORTC Lung Cancer Group.
[v] Representative of the EORTC Lymphoma Group.
[w] Central European Cooperative Oncology Group (www.cecog.org).
[x] Representative of the EORTC Radiation Oncology Group.

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In Europe, prophylactic treatment with granulocyte-colony stimulating factors (G-CSFs), such as filgrastim (including approved biosimilars), lenograstim or pegfilgrastim is available to reduce the risk of chemotherapy-induced neutropenia. 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. The need for generally applicable, European-focused guidelines led to the formation of a European Guidelines Working Party by the European Organisation for Research and Treatment of Cancer (EORTC) and the publication in 2006 of guidelines for the use of G-CSF in adult cancer patients at risk of chemotherapy-induced FN. A new systematic literature review has been undertaken to ensure that recommendations are current and provide guidance on clinical practice in Europe. We recommend that patient-related adverse risk factors, such as elderly age ($\geqslant$65 years) and neutrophil count be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. It is important that after a previous episode of FN, patients receive prophylactic administration of G-CSF in subsequent cycles. We provide an expanded list of common chemotherapy regimens considered to have a high ($\geqslant$20%) or intermediate (10–20%) risk of FN. Prophylactic G-CSF continues to be recommended in patients receiving a chemotherapy regimen with high risk of FN. When using a chemotherapy regimen associated with FN in 10–20% of 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. Clinical evidence shows 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. Filgrastim biosimilars are also approved for use in Europe. While other forms of G-CSF, including biosimilars, are administered by a course of daily injections, pegfilgrastim allows once-per-cycle administration. Choice of formulation remains a matter for individual clinical judgement. Evidence from multiple low level studies derived from audit data and clinical practice suggests that some patients receive suboptimal daily G-CSFs; the use of pegfilgrastim may avoid this problem.

1. Introduction

Chemotherapy-induced febrile neutropenia (FN) is a potentially fatal complication of cancer treatment, when it heralds infection and sepsis, and is seen most often during the initial cycles of myelosuppressive therapy.[1–8] Prevention of FN reduces hospital admissions, antibiotic usage and the need for dose reductions or delays in chemotherapy administration, which are associated with a poorer cancer outcome.[9–13]

Prophylactic administration of daily granulocyte-colony stimulating factor (G-CSF; filgrastim [Neupogen®] and lenograstim [Granocyte®]) or once per cycle administration of the pegylated form of G-CSF (pegfilgrastim, [Neulasta®])[14–18] provides protection for patients at risk of FN. In 2005, a European Guidelines Working Party was set up by the European Organisation for Research and Treatment of Cancer (EORTC) to systematically review available published data and derive evidence-based recommendations on the appropriate use of G-CSF in adult patients receiving chemotherapy; they first published their recommendations in 2006.[19] Since then, changes have occured in several areas, including our improved understanding of predisposing factors, the development of risk models and the availability of appropriate scoring systems. The risk of FN is increased by the recent trend for using dose-dense treatment schedules and the incorporation of taxanes and targeted agents into widely used chemotherapy regimens. With regard to the use of daily G-CSF versus once-per-cycle pegylated G-CSF, additional evidence has emerged since publication of the last EORTC guidelines. In addition, two further filgrastim biosimilar molecules (daily G-CSF) have been approved in Europe: XM02 and EP2006. These molecules are marketed by various companies using different trade names: Ratiograstim® (filgrastim; XM02), Filgrastim ratiopharm, Ratiopharm GmbH; Biograstim (filgrastim; XM02), CT Arzneimittel GmbH; Tevagrastim® (filgrastim; XM02), Teva Generics GmbH; filgrastim Zarzio® (EP2006), Sandoz GmbH; and filgrastim Hexal® (EP2006), Hexal Biotech Forschungs GmbH.[20–25]

These developments highlight the need to reassess current evidence and to update the existing guidelines regarding the prophylactic use of G-CSF.

A stringent and standardised definition of FN helps unify patient management algorithms. Febrile neutropenia is defined as an absolute neutrophil count (ANC) of $<0.5\times10^9$/L, or $<1.0\times10^9$/L predicted to fall below 0.5×10^9/L within 48 h, with fever or clinical signs of sepsis.[26] Currently, the European Society for Medical Oncology (ESMO) defines fever in this setting as a rise in axillary temperature to >38.5 °C sustained for