

East Midlands Network Guideline for the G-CSF use in Adult Patients

Background

The treatment of many malignancies is associated with a high rate of infectious morbidity and mortality due to neutropenia, particularly in elderly patients¹.

The clinical and economic implications of this include:

- Increased risk of infection and subsequent complications including death
- Hospitalisation and associated increased use of diagnostic procedures and IV antibiotics
- Reduced Quality of Life
- Reduced chemotherapy dose and duration

The potential benefits of adjunctive therapy with G-CSFs, both to reduce and prevent neutropenia associated with chemotherapy and to enhance the outcome of peripheral blood progenitor cell (PBPC) grafting and bone marrow transplantation (BMT), are well documented.

The specific aims of G-CSF therapy should include:

- To prevent neutropenia-associated infection
- To avoid the necessity for chemotherapy dose reduction and/or delay
- To enhance outcome after consolidation chemotherapy
- To treat neutropenia-associated infection which is unresponsive to antibiotic therapy
- To mobilise PBPCs before collection – see local JACIE policy
- To stimulate stem cell proliferation after PBPC infusion or BMT (note: post PBPC use is not currently a licensed indication in the UK) – see local JACIE policy

Establishing the need for G-CSF therapy in Chemotherapy induced febrile neutropenia

It should be noted that various clinical trials have defined FN in different ways and so FN should be defined as per local policy.

The incidence of febrile neutropenia (and thus the need for G-CSF administration) depends upon a number of risk factors including the dose intensity of the chemotherapy, the prior history of the patient and other co-morbidity. Of particular relevance however is the relative myelotoxicity of the chemotherapy regimen.

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Guidelines for G-CSF use

1. Primary prophylaxis

Definition:

Administration of a G-CSF following first and all subsequent cycles of chemotherapy in order to avoid an initial episode of FN.

Recommendation:

Clinical trial data supports the use of G-CSF when the risk of febrile neutropenia (FN) is in the range of 20% or higher² (See appendix 1)

G-CSF should be **considered** for primary prophylaxis in patients at high risk of FN³

e.g.

- Elderly (>65 years)
- History of previous extensive chemotherapy or radiotherapy
- Pre-existing neutropenia or bone marrow involvement with tumour
- Co-morbidity potentially enhancing risk of infection
- AIDS related NHL
- Poor performance status (if chemotherapy is indicated)
- Adjuvant breast cancer FEC100 /FEC-T
- Germ cell malignancies
- Limited Stage Small Cell Lung Cancer chemotherapy

Clinicians should consider dose reduction the primary therapeutic option for patients receiving palliative chemotherapy

In addition, for regimens in which G-CSF forms an integral part in order to enhance cytotoxic potential (e.g. FLAG, CODOX-M/IVAC) G-CSF should be used as per protocol

2. Secondary prophylaxis (following a previous episode of neutropenia +/- infection)

Definition:

Administration of G-CSF in the cycle following an episode of FN, or severe neutropenia, and all subsequent cycles.

Recommendation:

Clinicians should consider dose reduction the primary therapeutic option for patients receiving palliative chemotherapy

G-CSFs for secondary prophylaxis are recommended for patients who experience a neutropenic complication from a prior cycle of chemotherapy; in a dose reduction/dose delay (as a result of prolonged neutropenia) would compromise disease free or overall survival.

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3. Management of febrile neutropenia

Recommendation:²

G-CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, G-CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have at least 2 prognostic factors that are predictive of poor clinical outcomes. High-risk features include:

- expected prolonged (> 10 days) and profound (< 0.1 x 10⁹/L) neutropenia
- age > 65 years
- uncontrolled primary disease
- pneumonia
- hypotension
- multi-organ dysfunction (sepsis syndrome),
- invasive fungal infection
- or being hospitalized at the time of the development of fever.

4. Adjunct to stem cell transplantation

Recommendations:¹

G-CSF is utilised for the mobilisation of stem cells for autologous and allogeneic transplantation. It should be continued until adequate harvest has been achieved. Patients undergoing stem cell mobilisation have a written protocol, which should be followed.

G-CSF should be considered for autologous transplant patients in accordance with local transplant protocols

In the setting of stem cell mobilisation, G-CSF should be clearly prescribed by brand name.

5. Acute myeloid Leukaemia,

Recommendations:¹

G-CSF use following initial induction therapy may be considered, though there has been no favorable impact on remission rate, remission duration, or survival. Patients > 55 years of age may be most likely to benefit from CSF use.

G-CSF use may be used after the completion of consolidation chemotherapy to potentially decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive post remission chemotherapy.

As yet there is no information about the effect of longer-acting pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical trials

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6. Acute lymphocytic leukaemia

Recommendation:¹

G-CSFs are recommended to reduce the severity of neutropenia following intensive phases of therapy

7. Myelodysplastic syndromes

Recommendations:^{1,2}

Though G-CSF use can increase the absolute neutrophil count in neutropenic patients with MDS, data supporting the routine, long-term, continuous use of G-CSF for this population are lacking.

GCSF is recommended alongside EPO in MDS patients with WHO subtype RARS to stimulate erythropoiesis, as EPO alone rarely works in this subgroup.

Intermittent administration of G-CSF may be considered in a subset of patients with severe neutropenia and recurrent infection only at a Consultant Haematologist's specific request.

8. Congenital neutropenia/ Severe cyclical neutropenia / autoimmune neutropenia

Recommendation:

G-CSF may be prescribed only at the Consultant Haematologist's specific request

9. Clinical trials

Use of G-CSF in clinical trials is to be undertaken according to the study protocol

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General Considerations

1. Dose, administration route, duration of therapy and monitoring

The administration protocol for each agent varies according to setting e.g.

Growth Factor	Setting	Initiation	Duration
G-CSF	Myelotoxic chemotherapy	24-72 hours after administration of chemotherapy, or as per local protocol	Continue until ANC $\geq 1 \times 10^9/L$ or as per local protocol
	High-dose therapy and autologous stem-cell rescue	As per local protocol	Continue until ANC $\geq 1 \times 10^9/L$ or as per local protocol
	PBPC mobilization	As per local protocol	Continue until last leukapheresis, as per local protocol

2. Special Comments on Comparative Clinical Activity of G-CSF Formulations

Biosimilar Products

Guidelines for approval of biosimilars have been issued by the EMEA⁴ and vary according to the product. In general, the approval of biosimilars is based on the demonstration of equivalent efficacy and safety to the innovator product in comparative studies. In the case of G-CSF, equivalence has to be demonstrated in the prophylaxis of severe cytotoxic chemotherapy-induced neutropenia and extrapolation of efficacy to the other indications of the reference product (e.g. mobilization of stem cells) is then allowed. Because there is a limited clinical database on approval of a biosimilar (500-600 patients app.), pharmacovigilance is becoming essential, particularly as only six-month follow up is needed for safety in registration studies.

Therefore the EBMT recommends evaluation of efficacy and safety data for stem cell mobilization before using biosimilar G-CSF in healthy donors. This can only be obtained by performing clinical trials with an adequate number of stem cell mobilization procedures with adequate follow up in autologous conditions. Until studies have been performed to provide the required efficacy and safety data, the EBMT does not recommend the use of biosimilar G-CSFs for mobilization of stem cells in healthy donors for stem cell transplantation.⁵ The same advice should be considered for autologous stem cell mobilisation.

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Pegylated G-CSF

It should be noted that pegylated G-CSF only possesses a marketing authorisation for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)⁶. This product is not funded through NHSE

Recommendations:

In all settings other than stem cell mobilisation, the different short acting formulations of G-CSF may be considered interchangeable

3. Choice of formulation

With the exception of stem cell mobilisation (see above), the choice of G-CSF formulation should be a local decision based upon factors including:

- procurement cost
- marketing authorisation
- service configuration
- patient factors

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Appendix 1

Chemotherapy Regimens with a published FN rate $\geq 20\%$ ^{1, 2, 3}

Acute Myeloid Leukaemia

FLAG

Breast Cancer

TAC

Germ Cell Tumours

BEP

EP

TIP

VIP

Head & Neck Cancers

Docetaxel + 5-Fluorouracil + Cisplatin

Non Small Cell Lung Cancer

Docetaxel + Carboplatin

Non-Hodgkins Lymphoma

DHAP

ESHAP

IVE

R-IVE

CODOX-M/IVAC

Ovarian Cancer

Paclitaxel

Small Cell Lung Cancer

ACE

CAV

Urothelial Cancer

MVAC

Please note that this list is not exhaustive and does not take into account individual patient factors

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- ² [2006 Update of ASCO Practice Guideline Recommendations for the Use of White Blood Cell Growth Factors: Guideline Summary; *Journal Of Oncology Practice* • Vol. 2, Issue 4; July 2006](#)
- ³ NCCN Practice Guidelines in Oncology; Myeloid Growth Factors; v 1.0, 2009
- ⁴ [EMA Committee For Medicinal Products For Human Use \(CHMP\); Annex To Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: On-Clinical And Clinical Issues - Guidance On Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor; 2006](#)
- ⁵ [EBMT Stance on the Approval of a G-CSF Biosimilar, 2009](#)
- ⁶ [Amgen, Summary of Product Characteristics last updated on the eMC: 17/07/2008](#)

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