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East Midlands Cancer Alliance

East Midlands Guideline for Use of G-CSF 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 patients[1].
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 higher[2] (See appendix 1)
G-CSF should be **considered** for primary prophylaxis in patients at high risk of FN[3]
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 e.g. FEC100 /FEC-T
- Docetaxel in hormone responsive Prostate Cancer
- Germ cell malignancies
- Limited Stage Small Cell Lung Cancer chemotherapy
- Cabazitaxel

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
Following a second neutropenic episode G-CSFs as secondary prophylaxis should be considered if a further dose reduction/dose delay (as a result of prolonged neutropenia) would compromise disease free or overall survival.

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 10^9/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

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

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

10. Dosing

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

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Pegylated G-CSF

Currently this product is not funded through NHSE although may be an alternative for specific indications if funded locally.

In all settings Choice of formulation

Short acting formulations of G-CSF may be considered interchangeable but should be prescribed /recorded by brand in accordance with MHRA guidelines and local protocols.

The choice of G-CSF formulation should be a local decision following discussion with commissioners based upon factors including:

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

References

Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update Thomas J. Smith et al
Journal of Clinical Oncology 2015 33:28, 3199-3212