



Guideline for the use of granulocyte-colony stimulating factor (G-CSF) in adult oncology and haematology patients

Document Control

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1 Introduction

Chemotherapy-induced febrile neutropenia is a serious side effect of cancer treatment and is not only a major risk factor for infection-related morbidity and mortality, but is also a significant dose-limiting toxicity. Patients developing severe (grade 3/4) or febrile neutropenia (FN) during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy schedule. This may impact on the success of treatment, particularly when treatment intent is either curative or to prolong survival⁽¹⁾. One method of reducing the incidence of severe or FN is through the prophylactic use of G-CSF. G-CSF may also be used to increase neutrophils in those patients experiencing severe prolonged neutropenic episodes after chemotherapy treatment or in those patients requiring mobilisation of peripheral blood stem cells for harvesting.

There are several brands of filgrastim including bio-similars available, e.g. Accofil™, Neupogen™, Nivestim™ and Zarzio™. Bio-similar filgrastim is accepted as clinically the same as branded G-CSF.

The national bone marrow transplant service has recommended against the use of biosimilar for PBSC until further evidence of effectiveness in this setting is available.

NHS England recommends the use of Biosimilars as first choice G-CSF in all settings where the Neupogen brand of filgrastim would otherwise have been used. The choice of use of biosimilar in place of standard G-CSF should be a local commissioning decision but should generally be the lowest price.

NHS England does not recommend routine use of longer-acting pegylated G-CSFs such as pegfilgrastim (Neupogen®) and Lipegfilgrastim (Lonquex®). An exception is made for a limited number of specific situations. Where a longer-acting G-CSF is required prescribers should select the most cost-effective treatment which in most cases will be the preparation with the lowest acquisition cost.

The aim of this guideline is to provide evidence-based guidance to clinicians and other health professionals on the rational prescribing and safe administration of G-CSF and to promote harmonisation of prescribing practice in the Northern Cancer Alliance. (Please note: these guidelines do not apply to acute leukaemia or paediatric patients – follow guidelines stated within the relevant trial protocol).

2 Indications for G-CSF use

G-CSF may be prescribed for the following indications, according to the criteria for G-CSF prescribing outlined in section 3:

- a. Chemotherapy support for regimens with curative/radical intent (primary/secondary prophylaxis).
- b. Supportive therapy for severe neutropenic sepsis.
- c. Peripheral blood stem cell mobilisation.
- d. Clinical trials where appropriate and stated within the trial protocol.

Note: Patients receiving palliative chemotherapy should not generally receive prophylactic G-CSF for chemotherapy support – manipulations to minimise neutropenic episodes and sepsis **must** initially include dose delay and/or dose reduction (refer to individual chemotherapy protocols for guidance) as there is no evidence that dose maintenance or escalation improves clinically important outcomes. The use of G-CSF in this setting must be approved on an individual patient basis according to local trust policies for named patient approval of expenditure.

3 Criteria for G-CSF prescribing

3.1 Criteria 1A: Chemotherapy support for regimens with curative/ radical intent: **Primary prophylaxis** (first and subsequent cycle use)

Chemotherapy patients should not routinely be prescribed prophylactic G-CSF after their first cycle of chemotherapy except in the circumstances described below.

Primary prophylaxis may only be considered for patients with a high overall risk (> 20%) of febrile neutropenia as defined below:

- Patients receiving myelotoxic chemotherapy with curative or radical intent (including adjuvant/neoadjuvant chemotherapy) and which has a documented incidence rate of FN of > 20% (see table 1)

Regimen	Tumour type	Documented FN risk	Reference
DHAP	NHL (relapsed)	48%	(1), (2)
ESHAP/ FLUDAP	NHL Hodgkins disease Multiple Myeloma (all relapsed)	30%	(1), (2)
All Docetaxel-based regimens (includes FEC-T)	Breast (Neo-adjuvant) Breast (adjuvant)	22-36%	(3), (4)
CODOX-M/ IVAC (+/-R)	Burkitts Lymphoma	>50%	(5)
Mini-BEAM	Hodgkins disease (relapsed)	54%	(6)

Table 1: Regimens with FN rate of >20%

Primary prophylaxis may also be considered in:

- Patients receiving myelotoxic chemotherapy with curative/radical intent (including adjuvant/neoadjuvant chemotherapy) and which has a documented incidence rate of FN of 10 – 20% (see table 2) **AND** any one or more of the following pre-disposing patient risk factors (1):
 - Patient age > 65 years
 - Poor performance status
 - Previous episodes of febrile neutropenia
 - Extensive prior treatment including large radiation ports
 - Administration of combined chemoradiotherapy
 - Bone marrow involvement by tumour-producing cytopenias
 - Poor nutritional status
 - The presence of open wounds or active infections
 - More advanced cancer
 - Other serious co-morbidities

Regimen	Tumour type
Epi-CMF (Epi only)	Breast
BEP	Germ cell
EP	Germ cell
Carbo/Etoposide	Germ cell
POMB-ACE	Germ cell
TIP	Germ cell
VIP	Germ cell
Stanford V	Hodgkins disease
CHOP 21	NHL
FMD	NHL
IVE	NHL (relapsed)
R-CHOP 21	NHL

Table 2: Regimens with FN rate of 10-20%

The G-CSF of choice for primary prophylaxis in CNTW Area Team is daily G-CSF in the form of the biosimilar Filgrastim.

Occasionally the use of a longer-acting pegylated G-CSF as primary prophylaxis may be considered e.g. patients who cannot be taught or are incapable to self-inject or for whom there is not a suitable carer available to inject with daily G-CSF.

GCSF dosage and administration guidelines in the prophylactic setting.

Because the kinetics of myelotoxicity and recovery of bone marrow function vary between cytotoxic agents and regimens, universal recommendations on this subject cannot be made. There is some evidence that treatment soon after chemotherapy may be more beneficial than later, although, of course, G-CSF is contraindicated within 24 hours of chemotherapy, when stimulation of progenitor cells in the presence of cytotoxics may actually worsen the myelotoxicity of the regimen. For cytotoxic drugs with a long half life, a longer interval may be required to avoid increased myelotoxicity.

A reasonable starting point for GCSF is to start not less than 24 hours and not more than 72 hours after cytotoxic treatment is completed. This ensures that the stimulus provided is present at a time when the bone marrow is regenerative and able to respond.

For solid tumour regimens, e.g. FEC-T the consensus agreement in the Northern Cancer Alliance is to start daily G-CSF 48 hours (two days) after chemotherapy.

G-CSF injections should continue until the neutrophil count has recovered to $> 1.0 \times 10^9/L$ on two consecutive days. This will normally require a minimum of 5 days of treatment, although consideration should be given to a minimum of 7 days for more myelosuppressive regimens – studies looking at NHL patients receiving myelosuppressive chemotherapy showed that patients receiving 5 doses of G-CSF had about 3 times the risk of febrile neutropenia and hospitalization than those who received a 10 day course (7,8). It is not expected that every patient has serial FBC tests, rather that adjustments to the duration of therapy are made based on clinical expertise and past response of the patient to GCSF.

See table 3 below for GCSF dosage and administration guidelines in the prophylactic setting.

Drug	Patient weight	Dose	Route	Frequency	Days to prescribe (see note 1)			
					Weekly chemo cycle	2 weekly chemo cycle	3 weekly chemo cycle	4 weekly chemo cycle
Biosimilar Filgrastim	<78kg ≥78kg	30MU 48MU	sc	Once daily	Initiate G-CSF 24 - 72hrs after administration of chemotherapy unless otherwise specified in the chemotherapy protocol Continue until after nadir and ANC ≥ 1.0 X 10 ⁹ /L or as per chemotherapy protocol.			
Lipegfilgrastim (Lonquex®) or Pegfilgrastim (Neulasta®)	All	6mg	sc	Single dose	Not recommended	One dose is recommended for each chemotherapy cycle, administered approximately 24 hours following cytotoxic chemotherapy		

Table 3: G-CSF Dosage and Administration Guidelines for patients fulfilling criteria 1A/1B

Note 1: The optimal timing and duration of G-CSF administration in the prophylactic setting has not been defined in haematological malignancies, however the recommendations above should be considered as a guide.

For solid tumour oncology daily prophylactic G-CSF should be given ONCE daily for SEVEN days starting TWO DAYS (48 hours) after chemotherapy.

3.2 Criteria 1B: Chemotherapy support for regimens with curative/radical intent:
Secondary prophylaxis (prophylactic use in subsequent cycles after initial episode(s) of severe and/ or febrile neutropenia)

Secondary prophylaxis should only be considered in patients:

- Receiving myelotoxic chemotherapy with curative or radical intent

AND where further treatment delays or dose reductions may compromise the intended treatment outcome, for example in any one of the following circumstances:

- Where two or more dose reductions have occurred due to neutropenia or febrile neutropenia after a chemotherapy cycle
- Where chemotherapy treatment is delayed on two or more occasions due to neutropenia or febrile neutropenia

Note: Dose modifications will be a reasonable alternative in many clinical situations.

Secondary prophylaxis may only be considered after one delay in chemotherapy treatment or one dose reduction due to an episode of neutropenia or febrile neutropenia for the following patient groups where dose reduction/ dose delay would compromise disease free or overall survival:

- Adjuvant breast cancer
- Lymphoma (non-hodgkins lymphoma or hodgkins disease)
- Germ cell malignancies
- Neo-adjuvant chemotherapy
- Limited stage small cell lung cancer
- Radical chemoradiation (where delay or omission of chemotherapy treatment during concurrent therapy may have a negative impact on disease control)
- Multiple myeloma

The G-CSF of choice for secondary prophylaxis in the Northern Cancer Alliance is daily G-CSF in the form of the biosimilar Filgrastim.

Occasionally the use of a longer-acting pegylated G-CSF as primary prophylaxis may be considered e.g. patients who cannot be taught or are incapable to self-inject or for whom there is not a suitable carer available to inject with daily G-CSF.

Refer to table 3 for G-CSF dosage and administration guidelines in the prophylactic setting.

3.3 Criteria 2: Supportive therapy for severe neutropenic sepsis

G-CSF must not be routinely prescribed for the treatment of patients with uncomplicated febrile neutropenia or afebrile neutropenia. G-CSF may only be prescribed for the supportive treatment of patients with severe febrile neutropenia in scenarios as defined below:

- Profound febrile neutropenia: defined as absolute neutrophil count (ANC) $< 0.1 \times 10^9/L$ and patient febrile

And any one of the following prognostic factors that are predictive of poor clinical outcome:

- Clinically unwell with signs such as hypotension, organ dysfunction etc indicating potential risk of septic shock
- Expected prolonged duration of neutropenia (> 10 days)
- Persistent pyrexia despite appropriate antibiotics/antifungals
- Uncontrolled primary disease
- Pneumonia
- Proven or suspected invasive fungal infection

Patients treated with a longer-acting pegylated G-CSF should not be treated with additional G-CSF. In addition, there is currently a lack of evidence for therapeutic (rather than prophylactic) use of longer-acting G-CSF (3).

Refer to table 4 for G-CSF dosage and administration guidelines in the neutropenic sepsis setting.

Table 4: G-CSF Dosage and Administration Guidelines for patients fulfilling criteria 2

Drug	Patient Weight or BSA	Dosage	Route	Frequency	Criteria for stopping treatment
Biosimilar Filgrastim	<78kg	30MU	sc	Once daily	Stop G-CSF once ANC $> 0.5 \times 10^9/L$ for at least two consecutive days
	≥ 78 kg	48MU			

Note: Longer-acting Pegylated G-CSF is not approved for use in this setting

3.4 Criteria 3: Peripheral blood stem cell mobilisation

3.4.1 Background

Guidelines for approval of biosimilars have been issued by the EMEA (9) 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 (10). The same advice should be considered for autologous stem cell mobilisation.

3.4.2 Dosing

For patients not in a study, Lenograstim (GRANOCYTE[®]) should be used at the dosing schedule in the manufacturers SPC. <http://www.medicines.org.uk/emc/medicine/8347/SPC>

Lenograstim (GRANOCYTE[®]) should be prescribed to all patients undergoing harvesting of peripheral blood stem cells.

Note: Longer-acting Pegylated G-CSF is not approved for use in this setting.

3.5 Criteria 4: Peripheral blood stem cell transplantation

3.5.1 Post peripheral blood stem cell transplantation

If indicated patients should receive biosimilar Filgrastim at the daily dosing schedule in the manufacturers SPC according to patients weight.

Note post-autograft patients are at >20% FN risk, use of G-CSF has the potential to save 1-2 bed days per transplant.

3.5.2 Duration of treatment

Autologous transplants - Stop the G-CSF after 2 consecutive days of neutrophils $>1.0 \times 10^9/l$.

Note: Longer-acting Pegylated G-CSF is not approved for use in this setting.

3.6 Criteria 5: Graft failure post stem cell transplantation

G-CSF may be prescribed to patients receiving chemotherapy with radical or curative intent who are being treated within a clinical trial and where G-CSF is recommended or allocated as part of the trial protocol.

In the setting of graft failure post stem cell transplantation (i.e. after satisfactory engraftment, neutropenia develops), support with a trial of haematopoietic growth factors may resolve the graft failure.

3.7 Criteria 4: Clinical trials where appropriate and stated within the trial protocol

G-CSF may be prescribed to patients receiving chemotherapy with radical or curative intent who are being treated within a clinical trial and where G-CSF is recommended or allocated as part of the trial protocol.

The G-CSF brand, dosage and administration schedule used within a clinical trial should be that recommended within the trial protocol.

4 Approval to prescribe GCSF

4.1 For all indications EXCEPT in peripheral blood stem cell mobilisation

Unless a regimen listed in sections 3.1 - 3.2 or specified in a chemotherapy protocol that has been agreed by the Network Chemotherapy Group a consultant oncologist/haematologist, associate specialist or specialist registrar must authorise G-CSF treatment according to the above recommendations but it may be prescribed by any member of the clinical team and the indication must be documented in the patient's medical notes.

4.2 For peripheral blood stem cell mobilisation

Any member of the haematology medical team may prescribe G-CSF according to the appropriate protocol for the particular patient.

4.3 Prescribing G-CSF

In order to ensure that the correct product is administered, it is vital to specify the brand of GCSF required on the prescription. We would suggest prescribing by brand name only.

5 References

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