Pan Birmingham NHS
Cancer Network

Guideline for the use of Granulocyte Colony Stimulating Factors (G-CSF) in Adult Haemato-Oncology Patients

Date Approved by Network Governance	July 2012

Date for Review	July 2015

Changes between versions 1 and 2

- Included information on the new factors that are available.
- Added therapeutic indication and clarified other indications such as primary prophylaxis became primary prophylaxis of neutropenia.
- Summarised sections and removed unnecessary indications.
- Updated references on guidelines and drugs.

ENDORSED BY THE GOVERNANCE COMMITTEE

1 Scope of the guideline

This guidance has been produced to make recommendations for the use of Granulocyte Colony Stimulating Factors (G-CSF) in adult patients undergoing chemotherapy for cancer.

2 Guideline background

Bone marrow suppression is among the most common toxicities encountered as a result of chemotherapeutic treatment of malignancy. It can result in life-threatening complications arising from neutropenia, thrombocytopenia and anaemia. In addition dose reductions and dose delays occurring as a result of neutropenia may compromise treatment outcomes. Guidelines for the use of G-CSF and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) have been published by the American Society of Clinical Oncology and the British Committee for Standards in Haematology.

3. Guideline statements

The use of G-CSF may be indicated for the following:

a) primary prophylaxis of neutropenia (see section 4)
b) secondary prophylaxis of neutropenia (see section 5)
c) therapeutic use in patients admitted with febrile neutropenia (see section 6)
d) as an adjunct to allogeneic or autologous progenitor cell transplantation (see section 7)
e) therapeutic use in patients who require G-CSF to maintain neutrophil count and reduce their risk of neutropenia due to an underlying condition or due to long term bone marrow suppression from heavy chemotherapy treatment
f) as an adjunct in AML consolidation to reduce antibiotic treatment and reduce hospital stay

4. Primary prophylaxis

4.1 Primary prophylaxis treatment is initiated before the occurrence of neutropenia when the expected incidence of neutropenia for a given regimen is ≥20%, or when there are additional factors such as bone marrow involvement, prior therapy, or active infection that increase the risk of neutropenic complications.

4.2 Patients with the following should be considered for primary prophylaxis:

a) Ewing's sarcoma
b) Osteosarcoma
c) AIDS-related NHL

4.3 In addition elderly patients with pre-existing neutropenia, poor performance status (American Society of Clinical Oncology guidelines[2] define elderly as 65 or over) should be considered for primary prophylaxis

5. Secondary prophylaxis

5.1 Secondary prophylaxis treatment is initiated during treatment after an occurrence of chemotherapy-induced prolonged neutropenia or febrile neutropenia. The patient may or may not have required dose delay as a result of the prolonged neutropenia. Where clinical data supports the necessity of maintenance of chemotherapy dose intensity G-CSF should be considered.

5.2 Secondary prophylaxis should be considered for patients with potentially curative treatment or in tumours where it is felt that dose reduction/dose delay for subsequent cycles of chemotherapy may compromise outcome.

5.3 Patients undergoing first line treatment for non-curative, palliative or non-surgical life enhancing treatments, where dose reduction or delay should be avoided, may also be prescribed G-CSF for secondary prophylaxis.

6. Therapeutic use

6.1 G-CSF is indicated for therapeutic use where patients with neutropenic fever on antibiotics are at high risk of developing septic complications i.e. those with documented pneumonia, fungal infections, hypertension, or multi-organ failure. It may also be indicated to treat neutropenia in patients with inherited bone marrow failure syndromes.

6.2 G-CSF may be considered in high risk patients with neutropenia and fever (i.e. fever >10 days, neutrophils ≤ 0.1 x 10^9/l) with uncontrolled primary disease, pneumonia, cellulitis, abscess, sinusitis, hypertension, multi-organ failure and invasive fungal infections, in elderly patients or those with post-treatment lymphopenia.

6.3 This guideline does not recommend the use of G-CSF in the following circumstances:

a) in the treatment of asymptomatic neutropenia in patients who are afebrile and well, except in inherited bone marrow failure syndromes or with an absolute neutrophil count of less than 0.1 x 10^9/l.
b) in the treatment of uncomplicated fever and neutropenia (i.e. fever of ≤ 10 days duration) with no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multi-organ failure or invasive fungal infection and no uncontrolled malignancy).

However, this is not precluded in circumstances where the Trust local policy support use to reduce antibiotic use or decrease length of stay as per section 3 f.

7. As an adjunct to allogeneic or autologous progenitor cell transplantation

7.1 G-CSF should be used for both the mobilisation of peripheral blood progenitor cell (PBPC) and for accelerated haematopoetic reconstitution after allogeneic and autologous PBPC transplantation or BMT.

7.2 G-CSF should be used in patients who require G-CSF to maintain neutrophil count and reduce their risk of neutropenia due to an underlying condition, or due to long term bone marrow suppression from heavy chemotherapy treatment.

8. Dose and administration

8.1 Doses should be rounded to the nearest vial or pre-filled syringe size. Treatment should be continued until neutrophils >1.0 x 10^9 /l on two consecutive days (see appendix 1 for comparison of individual products).

9. Further information

9.1 G-CSF is usually well tolerated; occasionally, localised reactions may be observed at the injection site.

9.2 Musculoskeletal pain and headaches may be a problem in some patients. Patients should be warned of these effects. This can be minimised by the use of mild analgesia e.g. paracetamol, non-steroidal anti-inflammatory drugs or mild opioids.

9.3 Other side effects are rare but may include transient hypertension, thrombocytopenia, disturbances in liver enzymes and serum uric acid, splenic enlargement. For a full list of potential side effects refer to product literature.

9.4 Pharmacists, doctors and nurses are reminded to report serious, rare, unusual or unexpected adverse drug reactions using the Yellow Card Scheme.

10. Products available

10.1 The Pan Birmingham Cancer Network does not support any particular brand of product (See appendix 1). Individual Trusts should make their formulary choice based on local suitability of product range and local price.

10.2 The use of Pegfilgrastim is supported only in circumstances where it is considered appropriate and cost effective.

10.3 If Trusts decide to use biosimilar G-CSF products then a risk assessment should be carried out prior to the change over. Trusts must be aware that the European Blood and Bone Marrow Transplantation Group advice is not to use biosimilars to mobilise stem cells in healthy donors, and they may wish to include all patients requiring mobilisation.

11. Patient information and counselling

11.1 All patients, and with their consent, their partners will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a clinical nurse specialist who is a member of the relevant MDT. The patient should have a method of access to their specific tumour site team at all times.

11.2 Access to psychological support will be available if required. All patients should undergo an holistic needs assessment and onward referral as required.

12. Palliative care

12.1 Palliative care services will be made available to all patients as deemed appropriate by the MDT.

13. Clinical trials

13.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.

13.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network.
Email: PBCRN@westmidlands.nhs.uk

13.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

14. Monitoring of the Guideline

14.1 Adherence to the Network guidelines may from time to time be formally monitored.

15. References

1. BCSH. Guidelines on the use of Colony Stimulating Factors in Haematological Malignancies. British Journal of Haematology 2003, **123** 22-33.
2. American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline Published in Journal of Clinical Oncology, Vol 24, No 19 (July 1), 2006: pp. 3187-3205
3. BNF edition no 61 March 2011

4. European Blood and Bone Marrow Transplantation Group (see website)
5. Neupogen SPC May 2011
6. Neulasta SPC November 2011
7. Granocyte SPC May 2011
8. Nivestim SPC January 2011
9. Ratiograstim SPC April 2011
10. Zarzi SPC August 2011

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Appendix 1

Comparison of Products

Approved Name	Lenograstim	Filgrastim	PegFilgrastim
Brand Name	**GRANOCYTE®**	**NEUPOGEN®**	**NEULASTA®**
Description	Recombinant human granulocyte-colony stimulating factor (rHuG-CSF)	Recombinant human granulocyte-colony stimulating factor (G-CSF)	Pegylated recombinant methionyl human granulocyte-colony stimulating factor
Presentations available	*Powder for recon.* 13.4 mu vial (105 microgram) 33.6 mu vial (263 microgram)	*Liquid* 30 mu in 1ml vial (300 microgram) 48 mu in 1.6ml vial (480 micrograms) *Pre-filled syringes* 30 mu in 0.5ml (300 microgram) 48 mu in 0.5ml (480 micrograms)	*Pre-filled syringes* 6 mg in 0.6ml
Dose for licensed indications	*Chemo-induced neutropenia* sc: 19.2 MIU/m^2 /day after myelosuppressive chemo until neutrophil count in acceptable range. Up to a maximum of 28 days. *Mobilisation of PBSC* sc or iv infusion 19.2 MIU/m^2 /day for 4-6 days.	*Chemo-induced neutropenia* sc 0.5 mu/kg/day after myelosuppressive chemo until neutrophil count in acceptable range. Up to 14 days in solid tumours, lymphomas and lymphoid leukaemias. Up to 38 days in AML. *Mobilisation of PBSC* sc or iv infusion. 1 mu/kg/day for 5-7 days. See product literature for dose modification according to response.	*Chemo-induced neutropenia* sc 6 mg per chemotherapy cycle administered 24 hours after chemotherapy. Not licensed in CML or MDS. Caution in acute leukaemia and myelosuppressive chemotherapy. *Mobilisation of PBSC* Not licensed

Filgrastim is available as a number of biosimilars including Nivestim, Ratiograstim,and Zarzo. They are all licensed for use in mobilisation, chemo-induced neutropenia, and idiopathic neutropenia. They are available in liquid format as pre filled syringes. They are all available as two different doses except Nivestim which is also available as as a low dose injection. They are *recombinant methionylated human granulocyte-colony stimulating factor (G-CSF) produced in* E. coli *by recombinant DNA technology.*