
Practice Guideline:

Clinical Guide

**Recommendations for Filgrastim Use in Adults by
Disease Site**

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CCMB Practice Guideline

Clinical Guide

Developed by: Breast, CNS, Gastrointestinal, Genitourinary, Gynecologic-Oncology, Hematology, Leukemia and Bone Marrow Transplant, Lymphoproliferative, Sarcoma and Thoracic Disease Site Groups

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes in terms of survival and quality of life through the development, dissemination, implementation, and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This clinical guide was approved by the Breast, CNS, Gastrointestinal, Genitourinary, Gynecologic-Oncology, Hematology, Leukemia and Bone Marrow Transplant, Lymphoproliferative, Sarcoma and Thoracic Disease Site Groups.

Purpose

This document is intended as a guide to facilitate an evidence-informed, shared approach to the appropriate use of filgrastim in adults.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers, and dieticians at CCMB, CCPN sites, Uniting Primary Care Oncology Network (UPCON) clinics, and WRHA Community Oncology Program sites.

Disclaimer

Use of this clinical guide in any setting should not preclude use of the practitioner's independent clinical judgment; nor should it replace consultation with the appropriate oncology specialty when indicated (example: medical or radiation oncology, pharmacy, nursing, etc.). Clinicians are expected to apply the recommendations within boundaries of professional standards and scope of practice, and according to level of training and experience.

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care, and ideally this should take place within the context of an inter-professional team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

This clinical guide document should be viewed as an evidence-informed practice tool, and as such, it does not represent an exhaustive text on the appropriate use of filgrastim in adults. Clinicians are advised to use it in their practice concomitantly with information from other evidence-informed sources.

I.0 Background

- 1.1 Neutropenia and its complications (ie. febrile neutropenia and infection) are major toxicities associated with myelosuppressive chemotherapy.¹
- 1.2 Adverse consequences of febrile neutropenia include hospitalization, use of antibiotics and delays in chemotherapy administration.
- 1.3 Prophylaxis is indicated in specified clinical situations. They are outlined throughout this document.
- 1.4 The outcomes of interest to gauge the use of filgrastim in cancer include rate of hospitalization, use of antibiotic therapy, delays in chemotherapy and adherence to guidelines by examining prescribing patterns.

2.0 Purpose

- 2.1 The purpose of this document is to provide guidance to ensure appropriate prescribing of the growth factor filgrastim.
- 2.2 The recommendations are stratified by each disease site group in order to help clarify the indications for which filgrastim should be used.

3.0 Definitions

Definitions

<p>Febrile Neutropenia (Neutropenic fever/sepsis syndrome)^{2,3}</p>	<p>Systemic infection in neutropenic patients is potentially life-threatening. Therefore, neutropenic fever/sepsis syndrome is considered a time-dependent condition in which early recognition of the cancer patient’s potential to have neutropenic sepsis is critical to successful management.</p> <p><i>Fever</i> is defined as a single oral temperature of greater than 38.3° C (101° F); or equal to or greater than 38.0° C (100.4° F) for equal to or greater than 1 hour.</p> <p><i>Neutropenia</i> is defined as an absolute neutrophil count (ANC) less than 500/mm³ or an ANC that is expected to decrease to less than 500 cells/mm³ during the next 48 hours.</p>
<p>Primary Prophylaxis</p>	<p>In context of this document: administering granulocyte-colony stimulating factor (G-CSF) prior to systemic therapy to prevent neutropenia and associated fever/sepsis from occurring.</p>
<p>Secondary Prophylaxis</p>	<p>In context of this document: administering G-CSF to patients who have experienced neutropenic fever/sepsis to prevent reoccurrence.</p>

4.0 Recommended Use of Biosimilar Filgrastim - Update 2017

Effective July 19th, 2017, the biosimilar filgrastim product Grastofil^{®4} is used preferentially for adult patients who require filgrastim. Patients with latex allergies will receive the filgrastim product Neupogen[®], available in a 300 mcg or 480 mcg vial strength.

5.0 Recommendations by Disease Site Group

Breast Disease Site Group

Metastatic Setting

1. Primary prophylaxis is NOT recommended in the metastatic setting. Patients who develop febrile neutropenia or persistent neutropenia should be dose-reduced first. Patients who still have neutropenic events despite dose reductions may be considered for secondary prophylaxis. When an equally effective alternate chemotherapy option is available, that should be considered.

Adjuvant and Neo-Adjuvant Setting

1. Primary prophylaxis with filgrastim is not mandatory for any chemotherapy regimen in the adjuvant setting. The following patients may be considered for primary prophylaxis as an option:
 - Patients receiving regimen containing DOCEtaxel 100 mg/m² (DOCEtaxel cycles only as part of FEC-D)
 - Patients 65 years of age or older, with co-morbidities
 - Patients with significant co-morbidities
2. The use of filgrastim can be considered in patients who develop a febrile neutropenic event while on an adjuvant or neo-adjuvant protocol.
3. Primary prophylaxis with filgrastim is mandatory for patients who receive treatment with **dose-dense** AC (DOXOrubicin and Cyclophosphamide) – PACLitaxel regimen.

CNS Disease Site Group

1. Primary and secondary prophylaxis may be considered for PCV or CLV regimens.

Gastrointestinal Disease Site Group

1. There are no Gastrointestinal Disease Site Group regimens that require primary prophylaxis with filgrastim.
2. Secondary prophylaxis with filgrastim is only recommended for patients treated with FOLFIRINOX only AFTER two dose reductions have been given.
3. Secondary prophylaxis with filgrastim is recommended for patients treated with FLOT regimen.

Gynecologic-Oncology Disease Site Group

1. Filgrastim is recommended for patients who receive dose-dense PACLitaxel and CARBOplatin regimens.
2. For palliative treatments of ovarian, uterine and cervical cancer: dose reductions or cycle length extension is recommended rather than filgrastim usage.
3. There may be other regimens that are used occasionally and require filgrastim usage. Those would be considered on a case-by-case basis (non-formulary request).

Genitourinary Disease Site Group

1. The only genitourinary regimens where primary prophylaxis is recommended are TIP and VIP regimens for the treatment of germ cell tumors.
2. Secondary prophylaxis with filgrastim is recommended for patients treated with PEB for germ cell tumors.
3. All other usage of filgrastim in genitourinary regimens will require non-formulary approval with justification for use.

Hematology Disease Site Group

1. Myelodysplastic Syndromes (MDS) and Acute Leukemias: intervention with filgrastim is not recommended for the management of neutropenia that is unrelated to antineoplastic therapy.
2. Severe Congenital Neutropenia/Cyclic Neutropenia: patients with history of life threatening infection or with three episodes of infection within the previous 6 months, or individuals with chronic non-healing infections/ulcers.
3. Bone marrow biopsy confirmed agranulocytosis induced by drugs other than antineoplastic agents if there is no regeneration of bone marrow within 14 days following diagnosis and withdrawal of the suspected agent or if the patients become febrile while neutropenic.
 - Patients with agranulocytosis caused by peripheral destruction are specifically excluded from receiving filgrastim
 - Filgrastim must be prescribed by a hematologist
 - Filgrastim does not exceed 5 mcg/kg/day for 14 days. It is reasonable to strive for a post nadir ANC of $0.5 \times 10^9/L$ for 2 days or a single ANC of $10 \times 10^9/L$ for one day before discontinuation of filgrastim
4. Idiopathic (autoimmune) neutropenia - if complicated by increased frequency of infections. Recommendation for filgrastim required by a hematologist.

Leukemia and BMT (Bone Marrow Transplant) Disease Site Group

Acute Leukemia

1. Acute Myeloid Leukemia
 - Filgrastim may be administered if described in the treatment protocol
 - Patients with acute promyelocytic leukemia are specifically excluded
2. Acute Lymphocytic Leukemia (ALL)
 - Filgrastim may be administered if described in the treatment protocol

Blood and Marrow Transplant

1. Mobilization of autologous or allogeneic peripheral blood progenitor cells for the purpose of hematopoietic cell transplantation.
 - Typical filgrastim dose 10 mcg/kg
2. Progressive neutropenia (ANC less than $0.5 \times 10^9/L$) during ganciclovir or valganciclovir therapy following allogeneic or autologous peripheral blood stem cell transplant: to permit at least 2 weeks of ganciclovir therapy.
3. Delayed engraftment or graft failure following allogeneic or autologous hematopoietic cell transplant.
 - Filgrastim dose does not exceed 5 mcg/kg/day for the first 14 days
4. Following autologous bone marrow or peripheral blood progenitor cell transplantation (ASCT) to accelerate neutrophil recovery.
 - If filgrastim is to be used post ASCT it should be commenced no earlier than Day +7 and the dose administered should not exceed 5 mcg/kg/day. It is reasonable to strive for a post nadir ANC of $0.5 \times 10^9/L$ for 2 consecutive days or a single ANC of $10 \times 10^9/L$ for one day before discontinuation of filgrastim

Lymphoproliferative Disease Site Group – Update 2017

Hodgkin Lymphoma

1. Routine use of filgrastim in ABVD protocol for Hodgkin lymphoma is not recommended. The use of filgrastim can be considered in patients who have developed a febrile neutropenic event while on ABVD.

Non-Hodgkin Lymphoma

1. Bendamustine-based chemotherapy regimens do not require filgrastim. The recommendation is to dose-reduce bendamustine.
2. All patients who receive Dose-Adjusted R-EPOCH are eligible to receive filgrastim as it is incorporated into this regimen. Peg-filgrastim is not an option in the Dose-Adjusted R-EPOCH protocol as the dose adjustments are studied with filgrastim only.
3. Routine use of filgrastim with R-CVP is not recommended.
4. Routine use of filgrastim for primary prophylaxis in patients treated with GDP (with or without ritUXimab). The use of filgrastim as secondary prophylaxis is permitted for patients who develop a febrile neutropenic event and are treated with curative intent. If neutropenia was an issue during first line therapy, then filgrastim should be made available for primary prophylaxis to patients receiving GDP **with the caveat that they are treated with curative intent.**
5. The Disease Site Group does not recommend routine use of filgrastim in all patients treated with CHOP, R-CHOP, CEOP or R-CEOP regimens. The use of primary prophylaxis can be considered in patients who are over 65 years of age OR in younger patients with HIV and other immunosuppressive disorders (i.e. due to chronic methotrexate). Patients are eligible for filgrastim as secondary prophylaxis if CHOP, R-CHOP, CEOP or R-CEOP regimens are used with curative intent.
6. Primary prophylaxis is recommended with the following regimens: ESHAP, R-ESHAP, ICE, R-ICE, DHAP, R-DHAP, GELOX, CHOEP, MATRIX, FERRERI protocol, R-CODOX-M and R-IVAC.

Multiple Myeloma

1. All usage of growth factor support for myeloma regimens will require approval via a non-formulary request with justification.

Chronic Lymphocytic Leukemia

1. All usage of growth factor support for chronic lymphocytic leukemia regimens will require approval on a case-by-case basis via a non-formulary request with justification. Usage of filgrastim is not recommended with fludarabine-based regimens.

Sarcoma Disease Site Group

1. Filgrastim is recommended for inpatient sarcoma protocols: ifosfamide and etoposide for Ewing's, ifosfamide and DOXOrubicin for soft tissue sarcoma, CAV for Ewing's sarcoma, CISplatin and DOXOrubicin for osteosarcoma and high dose methotrexate for osteosarcoma.

Thoracic Disease Site Group

1. There are no regimens that require filgrastim as primary prophylaxis.
2. Secondary prophylaxis with filgrastim is recommended for patients treated with FLOT regimen.
3. Any other request for filgrastim for use in a Thoracic regimen will require non-formulary approval.

6.0 References

1. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American society of clinical oncology clinical practice guideline update. *J Clin Oncol* 2015;33(28):3199-212.
2. Northern Ireland Cancer Network. NICAacute oncology clinical guidelines. December 2015 (version 1.9). Accessed January 6, 2015 from, <http://www.cancerni.net/content/nican-acute-oncology-clinical-guidelines-launched-december-2015>
3. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious disease society of America. *Clin Infect Dis* 2011; 52(4):e56-93.
4. Canadian Agency for Drugs and Technologies in Health (CADTH): Common Drug Review – Subsequent Entry Biologic Review Report for Grastofil:
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