Post Transplant Neutropenia – Filgrastim (G-CSF) Protocol October 2017

Background:
Solid organ transplant recipients commonly experience low white blood cell counts (neutropenia) post-transplant. The cause of neutropenia is usually due to bone marrow suppression effects of anti-rejection and antiviral transplant medications or infections such as cytomegalovirus (CMV) related to transplantation. Patients with very low neutrophil counts are at very high risk for severe infections which require hospital admission, antibiotics and therapy with filgrastim. The addition of filgrastim to BC Transplant’s drug formulary would enable transplant clinicians the ability to treat patients with severe neutropenia as outpatients, decreasing the risk of infection and rejection, and the costs associated with inpatient admission.

The management of neutropenia post-transplant involves a careful assessment of the cause(s) of neutropenia and adjustments in immunosuppressive regimens and/or anti-viral therapies if CMV is suspected as the cause of the neutropenia. The most common medication adjustment includes reduction in the anti-metabolite (mycophenolate/azathioprine) dose to allow for neutrophil count recovery. However, there are many cases where a reduction in anti-metabolite dose is not the optimal choice as it can pose an increased risk of graft rejection. Clinicians are challenged with balancing neutropenia and the risk of infection versus immunosuppression reduction and risk of graft rejection. In some clinical situations where the risk of rejection and the consequences of rejection are extreme, the use of filgrastim will allow the continuation of anti-rejection treatment.

Evidence for filgrastim use in solid organ transplants:
Although not extensively studied, filgrastim has been used to increase neutrophil counts in solid organ transplant patients. Schmaldienst et al studied 19 renal transplant patients that experienced leukopenia in the 2 weeks to 24 months after transplantation (1). In comparison to an age-matched historical control group, patients receiving filgrastim had shorter duration of leukopenia (1.29 versus 7 days), with fewer infections; in addition, there were no episodes of rejection 2 weeks following administration.

Turgeon et al retrospectively reviewed 50 renal or liver transplant patients (2). Of the 50 patients, 43 patients had a rise in the leukocyte count to greater than 5.0 X 10^9/L following filgrastim. In 81.6% of cases, filgrastim therapy allowed for recommended dosing of ganciclovir or valganciclovir for treatment of CMV-induced neutropenia. Most recently, an abstract presented by Poon et al at the American Transplant Congress 2016 demonstrated effective reversal of neutropenia in kidney transplant recipients without increasing the risk of rejection (3).

Protocol:
The BC Transplant Drug Strategy Advisory Committee, and PHSA leadership and Finance have approved the addition of filgrastim to the BC Transplant Drug Formulary. With the support of the various organ group specialists/clinicians, BC Transplant has established the proposed protocol as outlined in Appendix 1.

Clinicians are required to complete the data collection-prescription form (Appendix 2). The BC Transplant Pharmacy will dispense the filgrastim and fax the form to BC Transplant for data collation. An annual report will be presented to the Drug Strategy Advisory Committee summarizing the usage and clinical data. If a patient requires more than 2 courses in a 12 month period, please contact the pharmacist at BC Transplant.

References
Management of Neutropenia Post Transplant v2.2

Post transplant neutropenia could be related to CMV, mycophenolate, azathioprine, valganciclovir*, Septra (cotrimoxazole).
The primary transplant specialists should be consulted regarding changes in immunosuppression and the re-introduction of antimitabolites, Septra when neutropenia has resolved. Decreasing or stopping anti-rejection medications in the “high risk” for rejection patient needs careful consideration.

WBC < 2.5 and Neutrophil > 1
- D/C valganciclovir prophylaxis and monitor CMV VL if > 4-6 months post Tx. Continue valganciclovir* if for treatment. Check CMV VL
- Reduce MMF/AZA by 50%
- D/C Septra
- Repeat CBC in 1 week

If WBC stable and patient is well, continue to monitor
If WBC/neutrophils continues to decline

WBC < 2.5 and Neutrophil 0.5 to 1
- D/C valganciclovir prophylaxis and monitor CMV VL if > 4-6 months post Tx. Continue valganciclovir* if for treatment. Check CMV VL
- Reduce MMF/AZA by 50% (if not done already)
- D/C MMF/AZA
- D/C Septra
- Repeat CBC in 1 week

If WBC/ neutrophils still declining
- D/C MMF/AZA
- D/C Septra
- Repeat CBC in 1 week

If WBC stable and patient is well, continue to monitor
If WBC/ neutrophils still declining

WBC < 2.5 and Neutrophil < 0.5
- Drugs potentially causing neutropenia have been discontinued if feasible
- Afebrile and generally well
- Febrile/unwell
- Manage as outpatient
- Admit
- Filgrastim (GCSF) x 3 doses (Course #1)
- Repeat CBC in 3 and 7 days after last dose of filgrastim

If neutrophils continue < 0.5, hematology consult after second course of filgrastim

Once WBC > 4,0 and stable, re-introduce any of the medications that were held or dose reduced. Monitor closely.

*valganciclovir dose adjusted for renal function
WBC = white blood cell (10^9/L)
Neutrophil (10^9/L)
AZA = azathioprine
CMV VL = CMV viral load
MMF = mycophenolate
Appendix 2:
Filgrastim (G-CSF, Grastofil) Data Collection-Prescription

1. Provider/Clinic to complete data collection sections and to forward prescription to BC Transplant Pharmacy

2. BC Transplant Pharmacy to dispense and fax form to BC Transplant office Fax: 604-877-2111

Organ group: [ ] Heart [ ] Kidney [ ] Liver [ ] Lung [ ] Pancreas/Islet Requesting clinic: ________________________

Assessment: please include dose adjustments if applicable

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Indication(s) for filgrastim:

☐ Neutrophil < 0.5
☐ Febrile neutropenia
☐ Other: ____________________________

☐ If transplant medication adjustments cannot be made, please indicate reason: __________________________________________________________

Prescription: [ ] 1st course – recommend 300 mcg dose for first course
[ ] 2nd course

*If neutrophils not responding after 2nd course in a 12 month period, please consult BCT and hematology
*For pediatric patients at BC Children’s – please supply Neupogen brand filgrastim

[ ] filgrastim (Grastofil) 300 mcg SC daily X 3 days

[ ] filgrastim (Grastofil) 480 mcg SC daily X 3days

BCT ID: ________________________
Name: ________________________
PHN: ________________________

Prescriber signature: ________________________
Print Name: ________________________
College ID: ________________________
Date: ________________________

Pharmacy: Please fax completed form to BC Transplant office: Fax: 604-877-2111 Attn: Pharmacy Coordinator