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### **Class Update with New Drug Evaluation: Colony Stimulating Factors**

**Month/Year of Review:** January 2015

**PDL Class:** Colony Stimulating Factors (CSF)

**Source Document:** OSU Abbreviated Class Update: Colony Stimulating Factors<sup>1</sup>

**New Drug(s):** tbo-filgrastim (Granix™)

**End date of literature search:** Week 2, November 2014

**Date of Last Review:** September 2012

**Manufacturer:** Teva

#### **Current Status of PDL Class:**

- Preferred: filgrastim (Neupogen™), pegfilgrastim (Neulasta™), sargramostim (Leukine™)
- Non-Preferred: tbo-filgrastim (Granix™) pending review

#### **Research Questions:**

- Is there new evidence to change the previous recommendations regarding the efficacy, effectiveness or harms of colony stimulating factors (CSFs)?
- Is there evidence that tbo-filgrastim is superior to currently available CSFs for prevention of febrile neutropenia in non-myeloid malignancies following myelosuppressive chemotherapy?
- Is there evidence that tbo-filgrastim is safer than currently available CSFs?
- Are there subpopulations where tbo-filgrastim may be more effective or safer?

#### **Conclusions:**

- There is no new evidence to support changes to the previous recommendations regarding the efficacy, effectiveness or harms of CSFs.
- There is low quality evidence from 3 randomized controlled trials that tbo-filgrastim is equivalent to filgrastim for reduction in the duration of neutropenia and incidence of febrile neutropenia associated with myelosuppressive chemotherapy in chemotherapy naïve patients with breast cancer, non-Hodgkin lymphoma and lung cancer.<sup>2,3,4</sup>
- There is low quality evidence from 3 randomized controlled trials that tbo-filgrastim is equivalent to filgrastim for harms.<sup>2,3,4</sup>
- There is insufficient evidence regarding subpopulations where the use of tbo-filgrastim may be safer or more effective.

#### **Recommendations:**

- Place Granix™ (tbo-filgrastim) as a preferred product on the PDL.
- No DUE of CSFs necessary at this time to assess adherence to NCCN guidelines and OHP Guideline Note 11 due to low overall utilization.

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**Reason for Review:**

This class was last updated in September 2012.<sup>1</sup> Tbo-filgrastim was approved by the United States Food and Drug Administration (FDA) on August 29, 2012.<sup>5</sup> While approved in Europe as a “biosimilar,” it was approved by the FDA under a standard new biological license application.<sup>6</sup> Additionally, new myeloid growth factors practice guidelines have been published by the National Comprehensive Cancer Network,<sup>6</sup> and the National Institute of Health and Care Excellence.<sup>7</sup>

**Previous Conclusions/Recommendations (2012):**

- There is moderate level evidence filgrastim and pegfilgrastim both prevent febrile neutropenia and all-cause mortality compared to placebo in patients receiving chemotherapy for solid or non-myeloid malignancies.
- There is low level evidence pegfilgrastim lowers the risk of febrile neutropenia versus filgrastim RR 0.66 (95% CI 0.44-0.98).
- There is low level evidence use of a CSF (filgrastim, pegfilgrastim, or sargramostim) lowers the risk of infection mortality versus placebo when used for prophylaxis of febrile neutropenia in patients with acute myeloid leukemia receiving chemotherapy but comparative evidence is lacking.
- There was no evidence found comparing the filgrastim, pegfilgrastim or sargramostim for the other FDA approved indications.
- There is low level evidence supporting off-label use of CSFs for hepatitis C treatment-induced neutropenia as more effective than dose reduction in improving sustained virologic response.
- Continue to list all drugs as preferred due to lack of comparative evidence for indications other than for prophylaxis of febrile neutropenia in patients receiving chemotherapy for solid or non-myeloid malignancies.

**Background:**

There are currently four CSFs available in the US: filgrastim, tbo-filgrastim, pegfilgrastim, and sargramostim. Sargramostim is a granulocyte macrophage-colony stimulating factor (GM-CSF) which stimulates the proliferation of neutrophil, monocyte, red-blood cell and platelet precursors.<sup>8</sup> Filgrastim, tbo-filgrastim and pegfilgrastim are granulocyte-colony stimulating factors (G-CSF) which induce proliferation of neutrophils.<sup>8</sup>

Filgrastim,<sup>9</sup> tbo-filgrastim<sup>10</sup> and pegfilgrastim<sup>11</sup> are all indicated to prevent febrile neutropenia, typically in patients with non-myeloid malignancies undergoing myelosuppressive chemotherapy. Febrile neutropenia can have a dose-limiting effect on chemotherapy, resulting in interruption of therapy, hospitalizations and intensive antibiotics.<sup>6</sup> The benefit of primary CSF prophylaxis in reducing hospitalizations, the need for antibiotics and rates of neutropenic fever in adults has been established but the impact on survival is less clear.<sup>6</sup> Established guidelines identify patients at highest risk for complications from chemotherapy-induced febrile neutropenia.<sup>6</sup> However, as much as 28% of patients are treated outside of guideline recommendations to lower risk of complications of febrile neutropenia.<sup>12</sup> CSFs are not used prophylactically in all patients because of safety concerns regarding the risk of developing secondary myelodysplastic syndrome or acute myeloid leukemia and rare cases of splenic rupture, even in healthy stem cell donors.<sup>6</sup> The most consistently observed toxicity is bone pain.<sup>6</sup> Treating off-label chemotherapy-induced febrile neutropenia in patients with leukemia or myelodysplastic syndrome is controversial because of the increased risk of stimulating the cancerous cell lines.<sup>6</sup>

Filgrastim is also indicated to speed myeloid recovery (engraftment) in harvesting of peripheral blood progenitor cells for transplant and for other neutropenias (Table 1).<sup>9</sup> G-CSFs are also used off-label for neutropenia induced from Hepatitis C (HCV) treatment or from AIDs, aplastic anemia, and Crohn’s disease.<sup>9,10,11</sup>

Sargramostim is used primarily to speed engraftment after allogeneic or autologous bone marrow transplantation or following the harvesting of peripheral blood progenitor cells for transplant or graft.<sup>13</sup> Quick myeloid recovery (engraftment) in patients undergoing a bone marrow or peripheral blood progenitor cell transplant reduces the risk or duration of FN in both situations.<sup>13</sup>

Filgrastim<sup>9</sup> and sargramostim<sup>13</sup> are given daily subcutaneously (SQ) or by intravenous infusion and dosed to response for the chemotherapy cycle or transplantation. Tbo-filgrastim<sup>10</sup> is available as only a daily SQ formulation. Pegfilgrastim is a pegylated formulation of filgrastim and is dosed SQ one time per chemotherapy cycle.<sup>11</sup>

Tbo-filgrastim was approved in Europe on a biosimilar application to the reference drug filgrastim. However, in the United States it was approved on a standard biological application with clinical trials. Another drug, lipefilgrastim, is under currently review by the FDA on a biosimilar application to the reference drug pegfilgrastim.

Table 1: Colony stimulating factor indications

Drug	FDA Labeled Indications	Off-label indications
filgrastim (G-CSF) <sup>9</sup>	<ul style="list-style-type: none"> <li>- Febrile neutropenia, In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation; Prophylaxis</li> <li>- Febrile neutropenia, In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis</li> <li>- Febrile neutropenia, In patients with acute myeloid leukemia receiving chemotherapy; Prophylaxis</li> <li>- Harvesting of peripheral blood stem cells</li> <li>- Neutropenic disorder, chronic (Severe), Symptomatic</li> </ul>	<ul style="list-style-type: none"> <li>- Agranulocytosis</li> <li>- AIDS / Hep C- Neutropenia</li> <li>- Aplastic anemia</li> <li>- Febrile neutropenia</li> <li>- Febrile neutropenia, In myeloid malignancies following bone marrow transplant; Prophylaxis'</li> <li>- Infectious disease; Prophylaxis</li> <li>- Leukemia</li> <li>- Myelodysplastic syndrome</li> <li>- Neutropenia - Pre-eclampsia</li> </ul>
tbo-filgrastim (G-CSF) <sup>10</sup>	<ul style="list-style-type: none"> <li>- Neutropenia (Severe), In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis</li> </ul>	
pegfilgrastim (G-CSF) <sup>11</sup>	<ul style="list-style-type: none"> <li>- Febrile neutropenia, In patients with non-myeloid malignancies; Prophylaxis</li> </ul>	<ul style="list-style-type: none"> <li>- Harvesting of peripheral blood stem cells, Prior to autologous stem-cell transplantation</li> </ul>
sargramostim (GM-CSF) <sup>13</sup>	<ul style="list-style-type: none"> <li>- Allogeneic bone marrow transplantation, Myeloid reconstitution in HLA-matched related donors</li> <li>- Autologous bone marrow transplant, Myeloid reconstitution following transplant in patients with non-Hodgkin's lymphoma, Hodgkin's disease, and acute lymphoblastic lymphoma</li> <li>- Bone marrow transplant, Delay or failure of myeloid engraftment</li> <li>- Febrile neutropenia, In acute myelogenous leukemia following induction chemotherapy; Prophylaxis</li> <li>- Harvesting of peripheral blood stem cells</li> <li>- Peripheral blood stem cell graft, Autologous, myeloid reconstitution following transplant in patients mobilized with granulocyte macrophage colony stimulating factor</li> </ul>	<ul style="list-style-type: none"> <li>- Crohn's disease</li> <li>- Febrile neutropenia, In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis</li> <li>- Malignant melanoma</li> <li>- Myelodysplastic syndrome</li> <li>- Neutropenic disorder - Sepsis of the newborn</li> <li>- Pulmonary alveolar proteinosis</li> <li>- Wound care</li> </ul>

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) from July week 2 2012 to week 2 November 2014 assessing clinically relevant outcomes of filgrastim, tbo-filgrastim, pegfilgrastim or sargramostim to placebo or active controls was conducted with limits for humans and English. Search terms included filgrastim, tbo-filgrastim, pegfilgrastim, sargramostim, XM-22, XM,-02, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor and febrile neutropenia or peripheral blood stem cell transplantation. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

After review of the citations from Medline and the manual searches, two updated guidelines, 2 RCTs comparing filgrastim to pegfilgrastim and 3 RCTs comparing tbo-filgrastim to placebo were included.

**Systematic Reviews:**

One systematic review of 3 clinical trials comparing tbo-filgrastim to filgrastim for prophylaxis of febrile neutropenia associated with myelosuppressive therapy for non-myeloid malignancy has been published but was unavailable in full-text at the time of writing this review.<sup>14</sup> The RCTs are reviewed individually below.

**New Guidelines:**

National Comprehensive Cancer Network<sup>6</sup> updated their consensus oncology practice guidelines for the use of myeloid growth factors (i.e. CSFs). The focus is to identify patients at high risk for febrile neutropenia for prophylactic CSF therapy. The guidelines align with Guideline Note 11 of the Prioritized List of Services (Appendix 1).<sup>15</sup> The guidelines identify sargramostim as having lower quality evidence for prophylaxis of febrile neutropenia in the oncology setting. It updates recommendations of timing of pegfilgrastim administration but makes no recommendation as to which of the remaining three products to use preferentially. It includes a new section on tbo-filgrastim.

The NICE pathway for prevention of neutropenic sepsis in cancer patients was updated in 2014.<sup>7</sup> The only mention of CSFs was “Do not routinely offer G-CSF for the prevention of neutropenic sepsis in adults receiving chemotherapy unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity.”

**Randomized Controlled Trials:**

*Table 2: Potentially relevant comparative trials*

Study	Comparison	Population	Primary Outcome	Results
Cesaro S., et al. <sup>16</sup> RCT, open label, non-inferiority Δ=3 days	32 patients got pegfilgrastim 100mcg/kg x 1 dose versus 29 patients got daily filgrastim 5mcg/kg/day x 9 doses	Pediatric patients who underwent autologous peripheral blood stem cell transplant. 20% had lymphoma/leukemia and 80% had solid tumors	mean number of days to recovery of polymorphonuclear cells	filgrastim: 10.48 (SD 1.57) pegfilgrastim: 10.44 (SD 2.44)  non-inferiority endpoint was reached
Shi Y-K, et al. <sup>17</sup>	Arm 1 (n=173): single dose of	Adults with malignant solid	rate of protection against	“In cycle 1, the rates of protection

RCT, open-label, crossover, non-inferiority study ( $\Delta$ not reported)	pegylated filgrastim 100 $\mu\text{g}/\text{kg}$ in cycle 1 and daily doses of filgrastim 5 $\mu\text{g}/\text{kg}/\text{day}$ in cycle 2 Arm 2 (n=164): daily doses of filgrastim 5 $\mu\text{g}/\text{kg}/\text{day}$ in cycle 1 and a single dose of pegylated filgrastim 100 $\mu\text{g}/\text{kg}$ in cycle 2	tumors, chemotherapy-naïve; life expectancy of >3 months, normal bone marrow function	grade 4 neutropenia after chemotherapy	were 89.7% (pegylated filgrastim) and 89.5% (filgrastim). In cycle 2, no episodes of grade 4 neutropenia occurred.” “The protective rates of pegylated filgrastim did not differ significantly from the protective rates of filgrastim.”
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**New Safety Alerts, Indications:**

No new safety alerts.

**New Drug Evaluation:** tbo-filgrastim

The FDA approved tbo-filgrastim based upon 2 Phase I<sup>5,18</sup> and 3 Phase 3 studies.<sup>2,3,4</sup> Only del Giglio A, et al.<sup>2</sup> was a pivotal, equivalence study with the remaining two being safety studies that also evaluated efficacy outcomes.<sup>3,4</sup>

*FDA approved indications:* Prophylaxis of febrile neutropenia, in patients with non-myeloid malignancies following myelosuppressive chemotherapy.

*Potential Off-label Use:* Treatment and prevention of neutropenia from other causes, peripheral blood stem cell transplantation and other indications listed in Table 1.

*Clinical Efficacy Data:* Tbo-filgrastim was compared to filgrastim in patients with breast cancer,<sup>2</sup> non-Hodgkin lymphoma<sup>3</sup> and lung cancer<sup>4</sup> taking myelosuppressive chemotherapies. The studies were of poor to fair quality due to lack of complete blinding, no description of randomization processes and lack of power analyses. The safety studies did not identify a primary outcome and considered efficacy outcomes exploratory. Tbo-filgrastim was superior to placebo on the outcome of duration of severe neutropenia, defined as defined as the number of days with grade 4 neutropenia with an ANC <0.5  $\times$  10<sup>9</sup>/L. (1.1 days versus 3.8 days, p <0.0001). No difference was found between tbo-filgrastim and filgrastim in any of the studies for the outcomes of duration of neutropenia and incidence of febrile neutropenia.

*Clinical Safety:* The FDA safety review notes that 750 patients and healthy volunteers have received one dose of tbo-filgrastim. Bone pain was observed in 24% of patients on tbo-filgrastim and 31% of patients on filgrastim.<sup>18</sup> No new safety concerns were raised and the safety profile of tbo-filgrastim was equivalent to that of filgrastim.<sup>18</sup>

**COMPARATIVE CLINICAL EFFICACY**

**Relevant Endpoints:**

- 1) Mortality
- 2) infections requiring treatment

**Primary Study Endpoint:**

- 1) Mean duration in days of severe neutropenia in cycle 1
- 2) Incidence of observed febrile neutropenia

3) Withdrawal due to adverse events

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Outcomes	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
del Giglio A, et al. <sup>2</sup>  RCT; Phase 3;  52 centers; 10 countries (researchers from South America & Eastern Europe)  Dec. 2004 to Sep. 2005	1. tbo-filgrastim (T): 5 mcg/kg/day  2. Neuopogen™ (N) 5 mcg/kg/day  3. placebo (P) - switched to T after cycle 1.  Starting one day after chemo-therapy, patients received daily injections for 5-14 days; stopped when an ANC of $\geq 10 \times 10^9/L$ after nadir was reached.  Patients underwent a maximum of 4 -3 week cycles of doxorubicin 60 mg/m <sup>2</sup> (i.v. bolus injection) and docetaxel 75 mg/m <sup>2</sup> (at least 1 hour infusion).	<u>Demographics:</u> Female: >99% Age: 51 (25-75) Caucasian: 85% BMI: 28 kg/m <sup>2</sup> Cancer Stage II: ~22% III: ~53% IV: ~25%  <u>Inclusion Criteria:</u> $\geq 18$ years old - breast cancer high risk stage II, III or IV (per AJCC) -planned/eligible to receive treatment with docetaxel / doxorubicin - ANC $\geq 1.5 \times 10^9/L$ -platelet count $\geq 100 \times 10^9/L$ -adequate cardiac function (LVEF $\geq 50\%$ as assessed by ECG <4 weeks prior to randomization) - ALT/AST <2.5 $\times$ ULN, alkaline phosphatase <5 $\times$ ULN, bilirubin <ULN, - Scr <1.5 $\times$ ULN.  <u>Exclusion Criteria:</u> -not reported	<u>ITT:</u> T:140 N:136 P:72  <u>PP:</u> Not reported  <u>Attrition:</u> Not reported	<u>Primary Outcome:</u> Mean duration of severe neutropenia defined as the number of days with grade 4 neutropenia with an ANC <0.5 $\times 10^9/L$ . in cycle 1:  T: 1.1 days N: 1.1 days P: 3.8 days  Mean difference: 0.028 (95% CI 0.261, 0.316); p <0.0001 <sup>18</sup>  <u>Secondary Outcomes:</u> Incidence of observed febrile neutropenia  T: 12.1% N: 12.5% P: 36.1%	NA  NA	<u>Withdrawn due to Adverse Event:</u>  T: 2 (1.4%) N: 3 (2.2%) P: 4 (5.6%)  RR 0.69 (95% CI 0.12, 4.04)	NA	<b>Quality Rating:</b> Fair  <b>Internal Validity (Risk of Bias):</b> <u>Selection:</u> (Mod) "randomize" not described <u>Performance:</u> (Mod) - unblinded because T, N formulated in different volumes. <u>Detection:</u> (Low) investigator/assessor blinded; used objective outcomes <u>Attrition:</u> (Mod); equivalence trial ITT reported in tables; PP mentioned in text but not details. PP is recommended for equivalence trials. Attrition not reported.  <b>Applicability:</b> <u>Patient:</u> Patient group likely more healthy than typical patients <u>Intervention:</u> no description; assume same as commercially available. <u>Comparator:</u> Neupogen™ <u>Outcomes:</u> Objective, clinical outcomes but, unclear relationship to mortality. <u>Setting:</u> Unclear how standards of care in research sites compare to Oregon.  <b>Analysis:</b> First comparison was made between T versus P. If significant using 2-sided p<0.05 (ANCOVA), then equivalence between T and N was assessed using 2-sided 95% CI with a $\Delta \pm 1$ day.
Engert et al. <sup>3</sup> RCT; Phase 3	1. tbo-filgrastim (T) 5 mcg/kg/day	<u>Demographics:</u> Female: 48%	<u>ITT:</u> T: 63	<u>No primary outcome designated.</u>		<u>Withdrawals due to Adverse Event.</u>		<b>Quality Rating:</b> Poor

<p>safety study?</p> <p>29 centers in 8 countries (researchers from Eastern Europe &amp; South America)</p> <p>Dec. 2004 to Mar. 2006</p>	<p>2. Neuopogen™ 5 mcg/kg/day</p> <p>x 5-14 days for first cycle. All patients received T in subsequent cycles.</p> <p>Study drug had to be stopped when an ANC of <math>\geq 10 \times 10^9/L</math> after nadir was reached.</p> <p>Patients got a maximum of 6 – 3 week cycles of chemo.</p>	<p>Age: 53 (18-83) Caucasian: 88% BMI: <math>\sim 26 \text{ kg/m}^2</math></p> <p><u>Inclusion Criteria:</u> -<math>\geq 18</math> years old -aggressive NHL - planned/eligible to receive CHOP -life expectancy <math>&gt;6</math> months - IPI score <math>\leq 3</math> - ANC <math>\geq 1.5 \times 10^9/L</math> -platelet count <math>\geq 100 \times 10^9/L</math> -adequate hepatic, cardiac, and renal function for the chemotherapy regimen.</p> <p><u>Exclusion Criteria:</u> Not reported.</p>	<p>N: 29</p> <p><u>PP:</u> Total: 76 (17.4% non-adherence rate)</p> <p><u>Attrition:</u> Total: 1 (0.1%)</p>	<p>Mean duration of severe neutropenia defined as the number of days with grade 4 neutropenia with an ANC <math>&lt; 0.5 \times 10^9/L</math> in cycle 1:</p> <p>T: 0.5 days N: 0.2 days p-value = 0.1055</p> <p>Incidence of observed febrile neutropenia during first cycle:</p> <p>T: 11.1% N: 20.7% p-value 0.1232</p>	<p>NA</p> <p>NA</p>	<p>Total: 5 (5.4%) not reported separately</p>	<p>NA</p>	<p><b>Internal Validity (Risk of Bias):</b> <u>Selection:</u> (Mod) “randomized” without description. <math>&gt;10\%</math> differences noted in gender, NHL types between groups. <u>Performance:</u> (Mod) administered by unblinded personnel as formulations looked different. <u>Detection:</u> (Low) investigator/assessor blinded; objective outcomes <u>Attrition:</u> ITT used; multiple outcomes increases potential for <math>\alpha</math>-error; small sample size increases potential for <math>\beta</math>-error for safety. No sample size calculation provided.</p> <p><b>Applicability:</b> <u>Patient:</u> patients likely more healthy than typical NHL patient. <u>Intervention:</u> no description; assume same as commercially available. <u>Comparator:</u> Neuopogen™ <u>Outcomes:</u> Objective, clinical outcomes but, unclear relationship to mortality. <u>Setting:</u> Unclear how standards of care in research sites compare to Oregon.</p> <p><b>Analysis:</b> All analyses of efficacy endpoints were done without alpha adjustment and were interpreted as descriptive/exploratory analyses.</p>
<p>Gatzemeier et al. <sup>4</sup></p> <p>RCT, Phase 3 Safety study?</p> <p>47 centers and 11 countries (researchers from Eastern Europe &amp;</p>	<p>1.tbo-filgrastim (T) 5 mg/kg/day</p> <p>2. Neuopogen™ (N) 5 mg/kg/day</p> <p>X 5-14 days for first cycle then all patient received T thereafter.</p> <p>Study drug had to be stopped when an</p>	<p><u>Demographics:</u></p> <p>Female: 22% Age: 58 (34-78) Caucasian: 95% BMI: <math>24 \text{ kg/m}^2</math></p> <p><u>Inclusion Criteria:</u> <math>\geq 18</math> years old -small cell or non-small cell lung cancer -planned platinum-</p>	<p><u>ITT</u> T: 160 N: 80</p> <p><u>PP</u> “219 (91.3%) completed cycle 1”</p> <p>Attrition not reported.</p>	<p><u>No primary outcome designated.</u></p> <p>Mean duration of severe neutropenia defined as the number of days with grade 4 neutropenia with an ANC <math>&lt; 0.5 \times 10^9/L</math> in cycle 1:</p> <p>T: 0.5 days N: 0.3 days p-value not reported</p>	<p>NA</p>	<p>31 patients (13.1%) discontinued the study due to a adverse event (differential not reported)</p>	<p>NA</p>	<p><b>Quality Rating:</b> Poor</p> <p><b>Internal Validity (Risk of Bias):</b> <u>Selection:</u> (Mod) “randomized” without description. Groups similar at baseline. <u>Performance:</u> (Mod) blinding not described <u>Detection:</u> (High) blinding not described <u>Attrition:</u> ITT used; multiple outcomes increases potential for <math>\alpha</math>-error; small sample size increases potential for <math>\beta</math>-error.</p>

<p>South America)</p> <p>Dec. 2004 to Dec. 2005</p>	<p>ANC of <math>\geq 10 \times 10^9/L</math> after nadir was reached.</p> <p>All patient got maximum of 6 – 3 to 4 week cycles</p>	<p>based chemotherapy -chemotherapy naïve or no more than 1 cycle. - ANC <math>\geq 1.5 \times 10^9/L</math> -platelet count <math>\geq 100 \times 10^9/L</math>, -adequate hepatic, cardiac, and renal function for the chemotherapy regimen.</p> <p><u>Exclusion Criteria:</u> Not reported.</p>		<p>Incidence of observed febrile neutropenia during first cycle:</p> <p>T: 15.0% N: 8.8% p-value not reported</p>	<p>NA</p>		<p><b>Applicability:</b> <u>Patient:</u> patients likely more healthy than typical NHL patients; overwhelmingly Caucasian. <u>Intervention:</u> no description; assume same as commercially available. <u>Comparator:</u> Neupogen™ <u>Outcomes:</u> Objective, clinical outcomes but, unclear relationship to mortality. <u>Setting:</u> Unclear how standards of care in research sites compare to Oregon.</p> <p><b>Analysis:</b> All analyses of efficacy endpoints were done without alpha adjustment and were interpreted as descriptive/exploratory analyses.</p> <p>The sample size of 240 has a 70% probability of detecting 1 case of AE which has an incidence rate of 0.5% or 91% for an incidence rate of 1%.</p>
<p><u>Key</u> [alphabetical order]: AJCC = American Joint Committee on Cancer; ALT/AST = alanine and aspartate aminotransferases; ANC = absolute neutrophil count; ARR = absolute risk reduction; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine) and prednisone; CI = confidence interval; ECG = electrocardiography; IPI = international prognostic index; ITT = intention to treat; LVEF = left ventricular ejection fraction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NHL = non-Hodgkin lymphoma; NNH = number, needed to harm; NNT = number needed to treat; PP = per protocol; RCT=Randomized Controlled Trial; RR = relative risk; SCr = serum creatinine; ULN = upper limit of normal.</p>							



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**Appendix 1: Oregon Health Plan List of Prioritized Services: Guideline Note 11<sup>15</sup>**

**GUIDELINE NOTE 11, COLONY STIMULATING FACTOR (CSF) GUIDELINES**

Lines 79,102,103,105,123-125,131,144,159,165,166,168,170,181,197,198,206-208,218,220,221,228,229,231,243,249,252,275-278,280,287,292,310-312,314,320,339-341,356,459,622

- A) CSF are not indicated for primary prophylaxis of febrile neutropenia unless the primary chemotherapeutic regimen is known to produce febrile neutropenia at least 20% of the time. CSF should be considered when the primary chemotherapeutic regimen is known to produce febrile neutropenia 10-20% of the time; however, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction should be explored in this situation.
- B) For secondary prophylaxis, dose reduction should be considered the primary therapeutic option after an episode of severe or febrile neutropenia except in the setting of curable tumors (e.g., germ cell), as no disease free or overall survival benefits have been documented using dose maintenance and CSF.
- C) CSF are not indicated in patients who are acutely neutropenic but afebrile.
- D) CSF are not indicated in the treatment of febrile neutropenia except in patients who received prophylactic filgrastim or sargramostim or in high risk patients who did not receive prophylactic CSF. High risk patients include those age >65 years or with sepsis, severe neutropenia with absolute neutrophil count <100/mcl, neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection, other clinically documented infections, hospitalization at time of fever, or prior episode of febrile neutropenia.
- E) CSF are not indicated to increase chemotherapy dose-intensity or schedule, except in cases where improved outcome from such increased intensity has been documented in a clinical trial.
- F) CSF (other than pegfilgrastim) are indicated in the setting of autologous progenitor cell transplantation, to mobilize peripheral blood progenitor cells, and after their infusion.
- G) CSF are NOT indicated in patients receiving concomitant chemotherapy and radiation therapy.
- H) There is no evidence of clinical benefit in the routine, continuous use of CSF in myelodysplastic syndromes. CSF may be indicated for some patients with severe neutropenia and recurrent infections, but should be used only if significant response is documented.
- I) CSF is indicated for treatment of cyclic, congenital and idiopathic neutropenia.