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Abbreviated Class Update: Colony Stimulating Factors

Month/Year of Review: September 2012

End date of literature search: July Week 2 2012

Current Status of PDL Class:

- Preferred Agents: FILGRASTIM (NEUPOGEN®), PEGFILGRASTIM (NEULASTA®), SARGRAMOSTIM (LEUKINE®)

Research Questions:

- Does new information change the previous recommendations regarding the efficacy and safety of colony stimulating factors (CSFs)?

Conclusions:

- There is moderate level evidence filgrastim and pegfilgrastim are considered equally efficacious and safe for prophylaxis of febrile neutropenia in patients receiving myelosuppressive chemotherapy for solid or non-myeloid malignancies
- There is moderate level evidence that filgrastim and pegfilgrastim are safe for use for prophylaxis of febrile neutropenia in patients receiving chemotherapy for solid or non-myeloid malignancies
- There is moderate level evidence sargramostim is considered efficacious for prophylaxis of febrile neutropenia in patients receiving chemotherapy receiving myelosuppressive chemotherapy for solid or non-myeloid malignancies, but sargramostim lacks the body of data of other CSFs
- There is insufficient evidence that sargramostim is safe for use for prophylaxis of febrile neutropenia in patients receiving chemotherapy for solid or non-myeloid malignancies
- There is low level evidence use of a CSF (filgrastim, pegfilgrastim, or sargramostim) is efficacious for prophylaxis of febrile neutropenia in patients with acute myeloid leukemia receiving chemotherapy
- There is insufficient evidence that use of a CSF (filgrastim, pegfilgrastim, or sargramostim) is safe for prophylaxis of febrile neutropenia in patients with acute myeloid leukemia receiving chemotherapy
- There is moderate level evidence that use of filgrastim and sargramostim are considered efficacious in speeding engraftment for cancer patients with a peripheral blood stem cell transplant
- There is insufficient evidence that use of pegfilgrastim is considered efficacious in speeding engraftment for cancer patients with a peripheral blood stem cell transplant
- There is insufficient evidence use of a CSF (filgrastim, pegfilgrastim, or sargramostim) is considered safe in speeding engraftment for cancer patients with a peripheral blood stem cell transplant

- 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

Recommendations:

- 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.
- Evaluate use of CSFs for hepatitis C and if inappropriate use is noted, bring back recommendation of prior authorization to the committee for consideration

Reason for Review:

In 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness of the CSFs. A December 2009 Provider Synergies Review was used as the evidence source.[1] Since this review, several systematic reviews and randomized controlled trials (RCTs) have been published, as well as updated guidelines from the National Comprehensive Cancer Network (NCCN), the European Organization for Research and Treatment of Cancer (EORTC), the European Association of the Study of the Liver (EAOSL), the Department of Veteran Affairs (VA), and the Canadian Agency for Drugs and Technologies in Health (CADTH).

Previous HRC Conclusions (2010):

- Evidence does not support a difference in efficacy or safety
- Recommend all agents without restriction

Background:

Three CSFs are available in the US: filgrastim, pegfilgrastim, and sargramostim. All are recombinant hematopoietic growth factors[2]; but differ in the cell lines they stimulate. Filgrastim and pegfilgrastim are granulocyte-colony stimulating factors which induce proliferation of neutrophils.[3-4] Sargramostim is a granulocyte macrophage-colony stimulating factor which stimulates the proliferation of neutrophil, monocyte, red-blood cell and platelet precursors.[5] Pegfilgrastim is a pegylated formulation of filgrastim and is dosed subcutaneously (SQ) one time only.[6] Filgrastim and sargramostim are available in SQ and intravenous (IV) formulations and are given once daily for SQ formulations or on multiple days by IV infusion.[7-8] All CSFs promote various responses from their target cells including activation and division, as well as some end-cell functions.[3-5]

Filgrastim is used to prevent and treat febrile neutropenia (FN), typically in patients with lymphomas, myelomas or solid tumors. It is indicated for FN prophylaxis in patients with non-myeloid malignancies undergoing myelosuppressive or myeloablative chemotherapy followed by bone marrow transplantation; and in acute myeloid leukemia (AML) patients receiving chemotherapy. It is used to treat non-cancer related Neutropenic disorder. Filgrastim is also indicated to speed myeloid recovery (engraftment) in harvesting of peripheral blood progenitor cells for transplant.[7] Pegfilgrastim is indicated for FN prophylaxis in patients with non-myeloid malignancies receiving chemotherapy, but is also used off-label for filgrastim's other indications: in AML patients receiving chemotherapy, Neutropenic disorder, and for engraftment after peripheral blood stem cell transplant.[6]

Like filgrastim and pegfilgrastim, sargramostim is most often used in patients with cancer to prevent FN but in a different way. Although it is indicated for use for FN prophylaxis in patients with AML, it is not approved for this use in patients with non-myeloid malignancies. Instead, 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.[8] 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.[9]

FN can have a dose-limiting effect on chemotherapy, resulting in interruption of therapy, hospitalizations and intensive antibiotics.[9] CSFs are not used prophylactically in all patients due to safety concerns regarding the risk of developing secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).[3] In addition, treating off-label chemotherapy-induced FN in patients with leukemia or MDS is controversial because of the increased risk of stimulating the cancerous cell lines.[9] CSFs are also used off-label for neutropenia induced from Hepatitis C (HCV) treatment or from AIDs, aplastic anemia, and Crohn's disease.[6-8] Please see Appendix 1 for all CSF indications.

Previously, the HRC concluded no difference in effectiveness or safety of filgrastim, pegfilgrastim, and sargramostim. All three were recommended for PDL placement without restriction.

Methods:
A Medline literature search was conducted beginning 2009 and ending July week 2 2012 for new systematic reviews and RCT's comparing filgrastim, pegfilgrastim or sargramostim for the treatment of neutropenia and peripheral blood progenitor cells transplantation. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, 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 for this class update. RCTs will be emphasized only if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, five new RCTs and six systematic reviews regarding the use of CSFs in cancer patients were identified; as were one new systematic review and RCT looking at CSF use during HCV treatment. All are included here. Five relevant guidelines from the NCCN, EORTC, EAOSL, VA, and CADTH were updated since the previous HRC review. Recommendations from the guidelines are listed here. Finally, one FDA Safety Alert was released for filgrastim. No new evidence was found regarding use in chronic neutropenic disorder, bone marrow transplant, or non-cancer related peripheral blood progenitor cell transplant, or any off-label indications with the exception of HCV treatment-induced neutropenia. Please see Appendix 1 for all CSF indications.

For use in chemotherapy-induced neutropenia:

Systematic Reviews:
Cooper et al[10] performed a poor-to-fair quality systematic review to look at the effectiveness of CSFs in reducing incidence of FN in adults with lymphoma or solid tumor undergoing myelosuppressive chemotherapy. Twenty studies were included with filgrastim, pegfilgrastim and lenograstim (CSF not available in US) used as prophylaxis compared with each other or placebo to prevent FN. Quality of the individual studies was not addressed. All three medications significantly reduced the risk of FN compared with placebo: pegfilgrastim RR 0.30 (95% CI 0.14-0.65), filgrastim RR 0.57 (95% CI 0.48-0.69). Five studies compared pegfilgrastim vs. filgrastim and demonstrated that pegfilgrastim reduced the risk of FN compared to filgrastim RR 0.66 (95% CI 0.44-0.98). Analysis for safety of CSF use was not included.

A poor-to-fair quality meta-analysis by Kruderer[11] also looked at the effectiveness of CSFs in reducing incidence of FN, infection-related mortality, and early mortality in adults with lymphoma or solid tumor undergoing chemotherapy. Fourteen of the 17 RCTs included in this systematic review were also used in the

above review. Quality assessment of individual trials was performed but not included in the published review. As with Cooper et al, this analysis found that both pegfilgrastim RR 0.077 (95% CI 0.034-0.175) and filgrastim RR 0.614 (95% CI 0.528-0.718) reduced the risk of FN versus placebo. Both medications decreased the risk of early mortality compared to placebo: pegfilgrastim RR 0.359 (95% CI .130-0.988), filgrastim RR 0.603 (95% CI 0.41-0.887). Only filgrastim decreased the risk of infection-related mortality: RR 0.529 (95% CI 0.304-.921). Pegfilgrastim and filgrastim were not compared with one another. Bone pain, the most common CSF side effect was also examined in the review. Bone or musculoskeletal pain was more common in CSF than placebo patients: RR 4.023 (95% CI 1.56-7.52).

Dynamed[3] reported new level-2 (mid-level) evidence that CSFs use was associated with reduced mortality but increased risk of AML or MDS in patients receiving chemotherapy for solid tumor or lymphoma. The fair quality systematic review by Lyman et al[12] analyzed 25 RCTs that used either filgrastim or lenograstim versus placebo in adult patients with lymphoma or solid tumors. Unlike the two reviews discussed above, this analysis included only studies with data on AML/MDS rates after CSFs treatment. The review found that patients treated with CSFs had a higher risk of developing a secondary malignancy: RR 1.92 (95%CI 1.19-3.07). CSF treatment was associated with a decrease in risk, however, for all-cause mortality: RR 0.897 (95% CI 0.857-0.938). Differences between lenograstim and filgrastim were not analyzed.

Heuser et al[13] examined the safety and efficacy of using CSFs agents prophylactically in patients with AML. Fourteen RCTs using filgrastim, pegfilgrastim, or sargramostim were included in this fair quality systematic review. Individual trial quality was uneven and there was significant heterogeneity between trials. Reviewers found using a CSF compared with placebo significantly decreased the time to engraftment (-4.13 days, 95% CI-4.23, -4.04) and length of hospitalization (-2.06 days, 95% CI-2.36, -1.76), but made no difference in infection related mortality. Other outcomes, rates of remission, disease-free and overall survival, were not significantly different between CSF and placebo patients. Analysis of CSF adverse events was not included.

Two new systematic reviews available from the Cochrane Collaboration examined the practice of giving CSFs to patients with leukemia. Sasse et al[14] found children with acute lymphoblastic leukemia (ALL) given prophylactic filgrastim or sargramostim had reduced incidence of FN episodes compared with placebo: RR 0.63 (CI 0.46-0.85). Prophylactic CSFs also significantly reduced the time to engraftment (-3.44 days, 95% CI -4.76, -2.12), length of hospitalization (-1.58 days, 95% CI -3.00, -0.15) and incidence of infections (RR 0.56, 95%CI 0.39-0.80). Although the authors intended to analyze adverse events, they were unable to due to a lack of uniformity in the side effects reported in the trials. This was a good quality review but with the limitation of a small number of heterogeneous studies decreasing the level of evidence.

The second Cochrane review, Gurion et al[15], looked at the safety outcomes of overall survival and all-cause mortality in AML patients given prophylactic filgrastim or sargramostim post-chemotherapy. Secondary outcomes included number of patients achieving complete remission, disease-free survival, incidence of FN and number of fungal and bacterial infections. No difference was found between treatment and placebo groups for any of the outcomes. There were slightly more discontinuations due to adverse events in the CSF vs. placebo groups (RR 1.33, 95% CI 1.00 -1.76). This was a good quality review but with the limitation of inclusion of a large number of studies with a high risk of bias.

A protocol[16] has been published from the Cochrane Collaboration to examine the use of CSFs in MDS. No date is given for expected completion.

New Guidelines:

European Organization for Research and Treatment of Cancer (EORTC) [17] *November 2010*

This guideline does not include sargramostim and is not intended for neutropenia due to leukemia, myelodysplastic syndrome, or HIV. Recommendations were graded based on the level of evidence. Grade A recommendations were taken from level I: evidence obtained from high quality sources (meta analyses, large RCTs). Grade B and C recommendations were consistent (B) or inconsistent (C) with findings from evidence levels II, III and IV: evidence obtained for level II was from at least one well-designed experimental or controlled trial, for level III from non-controlled experimental or well-designed observational studies, and for level IV from comparative, correlation, or case studies. Grade D recommendations have little to no systematic empirical evidence support.

- Patients' risk factors for FN should be considered evaluated prior to chemotherapy (Grade B).
- CSFs should be considered in patients with risk factors and chemotherapy regimens associated with a >10% increased risk of FN (Grade A/B).
- CSFs are recommended in patients with risk factors and chemotherapy regimens associated with a >20% increased risk of FN (Grade A/B).
- In situations where dose-dense /intensive chemotherapy strategies have survival benefits, prophylactic CSFs should be used (Grade A).
- If reductions in chemotherapy dose intensity/density are known to be associated with poor prognosis, primary CSF prophylaxis may be used to maintain chemotherapy (Grade A).
- For patients with solid tumors and ongoing FN, CSFs are indicated only in special situations: these are limited to those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infections, such as severe sepsis or septic shock (Grade B).
- Filgrastim and pegfilgrastim have demonstrated clinical efficacy and either of these agents should be used to prevent FN, where indicated. (Grade A).

The National Comprehensive Cancer Network (NCCN) [18] *Updated January 2012*

This guideline covers chemotherapy induced FN in patients with non-myeloid or solid tumors. Recommendations for patients with AML or MDS are covered in separate guidelines.[19-20] Recommendations are categorized as 1,2A, 2B, or 3. Category 1 is based upon high level evidence and uniform NCCN consensus; category 2A is based on lower-level evidence and uniform NCCN consensus; category 2B is based on lower-level evidence and some NCCN consensus; and a category 3 recommendation is based on any type of evidence and NCCN disagreement as the appropriateness of the intervention.

- Filgrastim and pegfilgrastim are considered to have equal efficacy (Category 1 recommendation for use).
- Due to the lack of evidence to support use in patients with non-myeloid or solid tumors, sargramostim is given a category 2b recommendation for use.
- Patients are stratified by a combination of personal risk factors (age, prior FN, or chemo) and chemotherapy regimen.
- Patients with risk of 10-20% of developing FN are considered for CSFs therapy (Category 2A recommendation).
- Patients with a risk of >20% of developing FN are recommended to start prophylactic CSFs (Category 2A recommendation).
- Patients who develop NF while on a CSF should continue the CSF (Category 2A recommendation).
- Patients without prophylactic FN who develop FN should be considered for CSF therapy only if they have risk factors (age, prior FN, severe infection or neutropenia) (Category 2A recommendation).
- CSFs are not recommended for prophylaxis in patients with MDS or AML[19-20] (Category 2A recommendations).

Randomized Controlled Trials:

The following RCTs were published after the systematic reviews included above. They were not rated for quality. RCT results supported the systematic review evidence.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results

Sebban C, et al. Eur J Cancer. 2012;48(5):713–720[21]	Pegfilgrastim vs. filgrastim	Adults with lymphoma or myeloma undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Mean duration of febrile neutropenia; safety and cost outcomes also examined	No difference found between the two for primary clinical and safety outcomes; pegfilgrastim was rated as more cost-effective
Beksac M, et al. Leukemia Research. 2011;35(3):340–345[22]	Filgrastim vs. placebo	Adults with acute myeloid leukemia (AML) undergoing high-dose chemotherapy	Short and long term differences in FN, hospitalization, antibiotic therapy and 3 years overall survival	No difference found between the two groups for any clinical outcome
Gerds A, et al. Biol. Blood Marrow Transplant. 2010;16(5):678–685[23]	Filgrastim vs. pegfilgrastim	Adults with lymphoma, myeloma, or solid tumor undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Time to neutrophils engraftment; NF, hospitalizations, transfusions and death were secondary outcomes	No difference found between the two for primary clinical and safety outcomes; pegfilgrastim was rated as more cost-effective
Ladenstein R, et al. J Clin Oncol. 2010;28(21):3516–3524[24]	Prophylactic filgrastim vs. symptom-triggered filgrastim	Children (ages 3-17) with neuroblastoma	Number of NF episodes; days with fever, in hospital, or on antibiotics were secondary outcomes	Prophylactic filgrastim had significantly ($p<0.05$) less FN episodes, days with fever, hospital and antibiotic days
Rifkin R, et al. Clin Lymph Mye Leuk. 2010;10(3):186–191[25]	Filgrastim vs. pegfilgrastim	Adults with lymphoma undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Time to engraftment	No difference found between the two for the primary outcome
Castagna L, et al. Ann Oncol. 2009;21(7):1482–1485[26]	Filgrastim vs. pegfilgrastim	Adults with lymphoma, myeloma, or solid tumor undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Duration of neutropenia; time to neutrophils engraftment, incidence of fever and infection were secondary outcomes	Pegfilgrastim is noninferior to filgrastim in the primary and secondary outcomes

For use in HCV treatment-induced neutropenia:

Systematic Reviews:

Tandon et al [27] conducted a fair quality systematic review to establish if use of filgrastim or lenograstim for HCV treatment-induced neutropenia impacted sustained virologic response (SVR) rates when compared to standard of care pegylated interferon-alfa PegINF dose reduction. The quality of studies included was poor, the majority of articles included were case series with one RCT, and provided low level evidence to conclude CSF should be used in HCV patients with neutropenia. The rate of SVR was 54.5% for patients given a CSF compared with 26.3% for dose reduction patients. Conclusions were drawn primarily from the

single, small RCT which was underpowered to determine any stastical difference in efficacy. The pooled risk from seven studies of an adverse event from CSF use was 13.1%. The most common adverse events were bone pain, rash, body aches and spleen enlargement; these were considered clinically insignificant.

New Guidelines:
These guidelines cover management and treatment of HCV including recommendations for supportive treatment for adverse events like neutropenia.

European Association of the Study of the Liver (EAOSL) [28] *Updated December 2011*
Recommendations in this guideline were graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. The strength of the recommendations are based on the quality of the underlying evidence and classified as high (A), moderate (B) or low (C). The GRADE system then offers two grades of recommendation: strong (1) or weak (2).

- There is no evidence that neutropenia during PegINF and ribavirin therapy is associated with more frequent infection episodes (C1).
- There is no evidence that the use of CSFs reduces the rate of infections and/or improves SVR rates (B1).
- EAOSL recognizes the use of CSFs during HCV treatment when the neutrophil count drops below 750–500/mm^3 is considered standard practice but finds there is insufficient evidence to recommend this practice

The Canadian Agency for Drugs and Technologies in Health (CADTH) [29] *Updated March 2012*
This is technically not a guideline but something CADTH frequently publishes, a Rapid Response Report. These reports provide recommendations based on a summary of the evidence. For this report, after a search including MEDLINE, PubMed, EMBASE, The Cochrane Library and other major international health technology agencies one fair-quality systematic review and one fair/poor quality open label RCT were included for analysis. These reports include an analysis of the quality of the studies and reviews chosen but do not rate or grade their recommendations.

- There is no clear evidence that would suggest an advantage of CSF intervention versus PegINF dose reduction as a strategy for managing neutropenia in patients with chronic hepatitis C infection treated with PegINF and ribavirin.

The Department of Veteran Affairs (VA) [30] *Updated May 2012*
Recommendations are classified by level of evidence: level A evidence is derived from RCTs or meta-analysis, level B from a single randomized or nonrandomized studies, and level C from expert opinion or standard-of-care. From there recommendations are further categorized in classes. For Class I, there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective. Class II recommendations have conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment; for Class IIa the weight of evidence/opinion is in favor of efficacy while for Class IIb efficacy is less well established by evidence/opinion. Class III is the lowest level recommendation for which there is evidence/general agreement that a diagnostic evaluation procedure/treatment is not useful or effective, and in some cases, may be harmful.

- Initial management of HCV treatment-related neutropenia should consist of a PegINF reduction for a neutrophil count <750/mm^3, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (Class I, Level C).

Randomized Controlled Trials:

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Talal AH, et al. *J. Acquir.*	Unspecified CSF vs.	HCV patients with comorbid HIV experiencing HCV treatment-	Difference in rate of SVR	No difference found between the two strategies for the primary outcome

Immune Defic. Syndr. 2011; 58(3):261–268[31]	PegINF dose reduction	induced neutropenia		

New Safety Alerts, Indications:

FDA Safety Alert May 2012: "Adverse Reactions" labeling changed to include the finding of decreased bone density and osteoporosis in pediatric SCN patients following post marketing surveillance. [32]

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Appendix 1: Colony stimulating factor indications[6-8]

Filgrastim (G-CSF)	Febrile neutropenia, In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation; Prophylaxis Febrile neutropenia, In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis Febrile neutropenia, In patients with acute myeloid leukemia receiving chemotherapy; Prophylaxis Harvesting of peripheral blood stem cells Neutropenic disorder, chronic (Severe), Symptomatic
Pegfilgrastim (G-CSF)	Febrile neutropenia, In patients with non-myeloid malignancies; Prophylaxis
Sargramostim (GM-CSF)	Allogeneic bone marrow transplantation, Myeloid reconstitution in HLA-matched related donors Autologous bone marrow transplant, Myeloid reconstitution following transplant in patients with non-Hodgkin's lymphoma, Hodgkin's disease, and acute lymphoblastic lymphoma Bone marrow transplant, Delay or failure of myeloid engraftment Febrile neutropenia, In acute myelogenous leukemia following induction chemotherapy; Prophylaxis Harvesting of peripheral blood stem cells Peripheral blood stem cell graft, Autologous, myeloid reconstitution following transplant in patients mobilized with granulocyte macrophage colony stimulating factor
CSF off-label indications	Crohn's disease Myelodysplastic syndrome AIDS induced neutropenia HCV treatment induced neutropenia Aplastic anemia Agranulocytosis

Appendix 2: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

Systematic Reviews

Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. *BMC Cancer*. 2011; 11(1):404.

Febrile neutropenia (FN) occurs following myelosuppressive chemotherapy and is associated with morbidity, mortality, costs, and chemotherapy reductions and delays. Granulocyte colony-stimulating factors (G-CSFs) stimulate neutrophil production and may reduce FN incidence when given prophylactically following chemotherapy. A systematic review and meta-analysis assessed the effectiveness of G-CSFs (pegfilgrastim, filgrastim or lenograstim) in reducing FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. G-CSFs were compared with no primary G-CSFs prophylaxis and with one another. Nine databases were searched in December 2009. Meta-analysis used a random effects model due to heterogeneity. Twenty studies compared primary G-CSFs prophylaxis with no primary G-CSFs prophylaxis: five studies of pegfilgrastim; ten of filgrastim; and five of lenograstim. All three G-CSFs significantly reduced FN incidence, with relative risks of 0.30 (95% CI: 0.14 to 0.65) for pegfilgrastim, 0.57

(95% CI: 0.48 to 0.69) for filgrastim, and 0.62 (95% CI: 0.44 to 0.88) for lenograstim. Overall, the relative risk of FN for any primary G-CSFs prophylaxis versus no primary G-CSFs prophylaxis was 0.51 (95% CI: 0.41 to 0.62). In terms of comparisons between different G-CSFs, five studies compared pegfilgrastim with filgrastim. FN incidence was significantly lower for pegfilgrastim than filgrastim, with a relative risk of 0.66 (95% CI: 0.44 to 0.98). Primary prophylaxis with G-CSFs significantly reduces FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. Pegfilgrastim reduces FN incidence to a significantly greater extent than filgrastim.

Kuderer NM. Meta-Analysis of Randomized Controlled Trials of Granulocyte Colony-Stimulating Factor Prophylaxis in Adult Cancer Patients Receiving Chemotherapy. In: Lyman GH, Dale DC, eds. *Hematopoietic Growth Factors in Oncology*.Vol 157. Boston, MA: Springer US; 2010:127–143.

Granulocyte colony-stimulating factor (G-CSFs) reduces the severity and duration of neutropenia associated with cancer chemotherapy [1–5]. In the pivotal phase III trial in patients with small cell lung cancer, patients were randomized to either G-CSFs or placebo following combination chemotherapy in a double-blind fashion [3]. A significant difference in the cumulative risk of febrile neutropenia (FN) between the control (77%) and the G-CSFs (40%) groups was observed despite the allowed use of secondary G-CSFs prophylaxis after an initial occurrence of FN in the control group ($P < 0.001$). Several additional clinical trials of prophylactic G-CSFs in patients with various malignancies receiving different treatment regimens have been reported [6–11].

Lyman GH, Dale DC, Wolff DA, et al. Acute Myeloid Leukemia or Myelodysplastic Syndrome in Randomized Controlled Clinical Trials of Cancer Chemotherapy With Granulocyte Colony-Stimulating Factor: A Systematic Review. *J Clin Oncol*. 2010; 28(17):2914–2924.

To evaluate the risk of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and overall mortality in patients receiving chemotherapy with or without granulocyte colony-stimulating factor (G-CSFs), a systematic review of randomized controlled trials (RCTs) was conducted. Electronic databases searched through October 2008 identified 3,794 articles for initial screening. Eligibility included solid tumor or lymphoma patients randomly assigned to chemotherapy with or without G-CSFs support, ≥ 2 years of follow-up, and reporting AML/MDS or all second malignancies. Dual blinded data extraction was performed. Relative risk (RR) and absolute risk (AR) estimates ± 95% CIs were calculated by the Mantel-Haenszel method. In the 25 eligible RCTs, 6,058 and 6,746 patients were randomly assigned to receive chemotherapy with and without initial G-CSFs support, respectively. At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSFs–treated patients, with an estimated RR of 1.92 (95% CI, 1.19 to 3.07; $P = .007$) and AR increase of 0.41% (95% CI, 0.10% to 0.72%; $P = .009$). Deaths were reported in 1,845 patients randomly assigned to G-CSFs and in 2,099 controls, for estimates of RR and AR decrease of 0.897 (95% CI, 0.857 to 0.938; $P < .001$) and 3.40% (95% CI, 2.01% to 4.80%; $P < .001$), respectively. Greater RR reduction for mortality was seen for both larger studies ($P = .05$) and greater chemotherapy dose-intensity ($P = .012$). Delivered chemotherapy dose-intensity and risk of AML/MDS are increased but all-cause mortality is decreased in patients receiving chemotherapy with G-CSFs support. Greater reductions in mortality were observed with greater chemotherapy dose-intensity.

Heuser M, Zapf A, Morgan M, Krauter J, Ganser A. Myeloid growth factors in acute myeloid leukemia: systematic review of randomized controlled trials. *Ann Hematol*. 2010; 90(3):273–281.

Randomized controlled trials (RCT) investigating administration of colony-stimulating factors (CSFs) during or after chemotherapy in acute myeloid leukemia (AML) patients have not been systematically reviewed. We performed a meta-analysis of all reported RCTs comparing prophylactic or concurrent use of CSFs in adult AML patients. Two reviewers extracted data independently. Summary estimates with 95% confidence intervals (CIs) were calculated using a fixed effects model. Fourteen RCTs ($n = 4,069$ patients) were identified investigating prophylactic CSFs administration. Time to neutrophil recovery (>500/μl) was significantly reduced in the CSFs group (−4.13 days; 95% CI, −4.23 to −4.04) as was the length of hospitalization (−2.06 days; 95% CI, −2.36 to −1.76). However, no significant reduction in infection-related mortality was observed in CSFs-treated compared with control patients (odds ratio (OR) 0.94; 95% CI, 0.8 to 1.1). Prophylactic CSFs administration did not impact complete remission (CR) rate or survival. Fourteen RCTs ($n = 4,518$ patients) were identified investigating administration of CSFs during chemotherapy. Summary estimates of CR, disease/event-free, or overall survival were not

significantly different for CSFs versus control patients. Prophylactic CSFs administration reduces the time to neutrophil recovery and length of hospitalization, but has no impact on documented infections or outcome. Economic analyses of prophylactic CSFs administration in AML patients are warranted.

Gurion R, Belnik-Plitman Y, Gafter-Gvili A, et al. Colony-stimulating factors for prevention and treatment of infectious complications in patients with acute myelogenous leukemia. In: The Cochrane Collaboration, Raanani P, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012.

Acute myelogenous leukemia (AML) is a fatal bone marrow cancer. Colony-stimulating factors (CSFs) are frequently administered during and after chemotherapy to reduce complications. However, their safety with regard to disease-related outcomes and survival in AML is unclear. Therefore, we performed a systematic review and meta-analysis to evaluate the impact of CSFs on patient outcomes, including survival. Objective: To assess the safety/efficacy of CSFs with regard to disease-related outcomes and survival in patients with AML. We conducted a comprehensive search strategy. We identified relevant randomized clinical trials by searching the Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, Issue 7), MEDLINE (January 1966 to July 2010), LILACS (up to December 2009), databases of ongoing trials and relevant conference proceedings. Randomized controlled trials that compared the addition of CSFs during and following chemotherapy to chemotherapy alone in patients with AML. We excluded trials evaluating the role of CSFs administered for the purpose of stem cell collection and/or priming (e.g. before and/or only for the duration of chemotherapy). Two review authors appraised the quality of trials and extracted data. For each trial, we expressed results as relative risk (RR) with 95% confidence intervals (CI) for dichotomous data. We analyzed time-to-event outcomes as hazard ratios (HRs). The search yielded 19 trials including 5256 patients. The addition of CSFs to chemotherapy yielded no difference in all-cause mortality at 30 days and at the end of follow up (RR 0.97; 95% CI 0.80 to 1.18 and RR 1.01; 95% CI 0.98 to 1.05, respectively) or in overall survival (HR 1.00; 95% 0.93 to 1.08). There was no difference in complete remission rates (RR 1.03; 95% CI 0.99 to 1.07), relapse rates (RR 0.97; 95% CI 0.89 to 1.05) and disease-free survival (HR 1.00; 95% CI 0.90 to 1.13). CSFs did not decrease the occurrence of bacteremias (RR 0.96; 95% CI 0.82 to 1.12), nor the occurrence of invasive fungal infections (RR 1.40; 95% CI 0.90 to 2.19). CSFs marginally increased adverse events requiring discontinuation of CSFs as compared to the control arm (RR 1.33; 95% CI 1.00 to 1.56). In summary, colony-stimulating factors should not be given routinely to acute myelogenous leukemia patients post-chemotherapy since they do not affect overall survival or infectious parameters including the rate of bacteremias and invasive fungal infections.

Sasse EC, Sasse AD, Brandalise SR, Clark OAC, Richards S. Colony-stimulating factors for prevention of myelosuppressive therapy-induced febrile neutropenia in children with acute lymphoblastic leukaemia. In: The Cochrane Collaboration, Sasse EC, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005.

Acute lymphoblastic leukaemia (ALL) is the most common cancer in childhood and febrile neutropenia is a potentially life-threatening side effect of its treatment. Current treatment consists of supportive care plus antibiotics. Clinical trials have attempted to evaluate the use of colony-stimulating factors (CSF) as additional therapy to prevent febrile neutropenia in children with ALL. Individual trials have not demonstrated significant benefit. Systematic reviews provide the most reliable assessment and the best recommendations for practice. Objectives: To evaluate the safety and effectiveness of the addition of granulocyte colony-stimulating factors (G-CSF) or granulocyte macrophage colony-stimulating factors (GM-CSF) to myelosuppressive chemotherapy in children with ALL in an effort to prevent the development of febrile neutropenia. Evaluation of number of febrile neutropenia episodes, length to neutrophil count recovery, incidence and length of hospitalisation, number of infectious disease episodes, incidence and length of treatment delays, side effects (flu-like syndrome, bone pain and allergic reaction), relapse and overall mortality (death). The search covered the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CANCERLIT, LILACS, and SciElo. We manually searched records of conference proceedings of ASCO and ASH from 1985 to 2003 and used the electronic databases of the ASCO and ASH web sites to search for abstracts from 2003 to September 2008, as well as databases of ongoing trials. We consulted experts and scanned references from the relevant articles. We looked for randomised controlled trials (RCTs) comparing CSF with placebo or no treatment as primary or secondary prophylaxis to prevent febrile neutropenia in children with ALL. Two authors independently selected and critically appraised studies and extracted relevant data. The end points of interest were: * Primary end points: number of febrile neutropenia episodes and overall mortality (death) * Secondary end points: time to neutrophil count recovery, incidence and length of hospitalisation, number of infectious diseases episodes, incidence and length of treatment delays, side effects (flu-like syndrome, bone pain and allergic reaction) and relapse. We conducted a meta-analysis of these end points and expressed the results as Peto odds ratios. For continuous outcomes we calculated a

weighted mean difference and a standardised mean difference. For count data, we conducted a meta-analysis of the logarithms of the rate ratios using generic inverse variance. We scanned more than 6800 citations and included six studies with a total of 333 participants in the analysis. There were insufficient data to assess the effect on survival. The use of CSF significantly reduced the number of episodes of febrile neutropenia episodes (Rate Ratio = 0.63; 95% confidence interval (CI) 0.46 to 0.85; P = 0.003, with substantial heterogeneity), the length of hospitalisation (weighted mean difference (WMD) = -1.58; 95% CI -3.00 to -0.15; P = 0.03), and number of infectious disease episodes (Rate Ratio = 0.56; 95% CI 0.39 to 0.80; P = 0.002). Despite these results, CSF did not influence the length of episodes of neutropenia (WMD = -1.11; 95% CI -3.55 to 1.32; P = 0.4) or delays in chemotherapy courses (Rate Ratio = 0.75; 95% CI 0.47 to 1.20; P = 0.23). Children with ALL treated with CSF benefit from shorter hospitalisation and fewer infections. However, there was no evidence of shortened duration of neutropenia nor fewer treatment delays. There was also no useful information about survival.

Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: systematic review and economic evaluation. *Journal of Viral Hepatitis*. 2011;18(7):e381–e393

Hepatitis C virus (HCV) treatment requires maximal adherence to pegylated interferon (Peg-IFN) and ribavirin to achieve a sustained virologic response (SVR). Neutropenia is the most common cause for Peg-IFN dose reduction. Our objectives were to evaluate the effectiveness, safety and cost-effectiveness of granulocyte colony-stimulating factor (G-CSF) versus Peg-IFN dose reduction for HCV therapy-associated neutropenia in treatment naïve adults. We conducted a systematic review to identify controlled trials and observational studies. Study selection, quality assessment and data extraction were completed independently by two investigators. Cost-effectiveness and cost-utility analyses compared G-CSF with dose reduction. Nineteen studies were included. In one trial, the SVR for those receiving G-CSF was 54.5% (95% CI: 34.7–73.1) compared with 26.3% (95% CI: 11.8–48.8) for dose reduction. The remaining studies were case series or retrospective cohorts and provided weak evidence for the relationship between SVR and G-CSF. The risk of adverse events, including infection, associated with G-CSF was low (13.1%; 95% CI: 8.0–20.8) and clinically insignificant. G-CSF had an incremental cost-effectiveness ratio of $41 701 per SVR achieved in genotype 1, and $16 115 per SVR achieved in genotype 2 or 3. Estimates were robust under a variety of resource and intervention scenarios. While administration of G-CSF may enable patients to remain on or resume optimal HCV therapy, there was weak evidence that this improves the likelihood of SVR compared with dose reduction. Adverse effects of G-CSF are mild. The economic evaluation was inconclusive.

Randomized Controlled Trials

Sebban C, Lefranc A, Perrier L, et al. A randomised phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study). *Eur J Cancer*. 2012; 48(5):713–720.

To evaluate in a multicentre randomised study the effect on duration of febrile neutropenia (FN), the safety and cost-effectiveness of a single subcutaneous pegfilgrastim injection compared with daily injections of filgrastim after peripheral blood stem cell transplantation in patients receiving high dose chemotherapy for myeloma and lymphoma. Patients were randomly assigned to a single dose of pegfilgrastim at day 5 (D5) or daily filgrastim from D5 to the recovery of absolute neutrophil count (ANC) to 0.5 G/L. Duration of FN, of neutrophil and platelet recovery, transfusion and antibiotic requirements were the main end-points of the study. Costs were calculated from D0 until transplant unit discharge. The incremental cost-effectiveness ratio was expressed as the cost per day of FN prevented. Probabilistic sensitivity analysis was performed by non-parametric bootstrap methods. Between October 2008 and September 2009, 10 centres enrolled 151 patients: 80 patients with lymphoma and 71 patients with myeloma. The mean duration of FN was 3.07 days (standard deviation (SD) 1.96) in the pegfilgrastim arm and 3.29 (SD 2.54) in the filgrastim one. Mean total costs were 23,256 and 25,448 euros for pegfilgrastim and filgrastim patients, respectively. There was a 62% probability that pegfilgrastim strictly dominates filgrastim. Pegfilgrastim after PBSC transplantation in myeloma and lymphoma is safe, effective when compared with filgrastim and could represent a cost-effective alternative in this setting.

Beksac M, Ali R, Ozcelik T, et al. Short and long term effects of granulocyte colony-stimulating factor during induction therapy in acute myeloid leukemia patients younger than 65: Results of a randomized multicenter phase III trial. *Leukemia Research*. 2011; 35(3):340–345.
This prospective multicenter phase III clinical trial was designed to assess efficacy and safety of G-CSFs as an adjunct to *de novo* AML remission induction therapy (www.clinicaltrials.gov. NCT00820976). Patients' characteristics were similar in both arms. G-CSFs improved severity and duration of leukopenia. Three-year OS were similar (25.6 ± 5.1% vs. 31.8 ± 5.6%) in both arms except for patients with myeloblastic features. Significant factors for better survival were the use of G-CSFs ($p = 0.049$), female sex ($p = 0.05$) and single induction cycle ($p < 0.001$) in multivariate analysis. Female patients performed better than male patients. Better survival obtained among female AML patients needs to be validated within the context of cytogenetic analysis.

Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologous peripheral blood stem cell transplantation. *Biol. Blood Marrow Transplant*. 2010; 16(5):678–685.
Nonrandomized trials suggest that pegfilgrastim, a pegylated granulocyte colony-stimulating factor, could be used in lieu of filgrastim after autologous peripheral blood stem cell transplantation. This phase III, randomized, double-blinded, placebo-controlled trial compared the efficacy, costs, and safety of single-dose pegfilgrastim (single 6 mg dose) versus daily filgrastim (5 microg/kg/day) for this indication. Seventy-eight patients, matched for age, sex, underlying disease, stage, and CD34/kg transplant dose were enrolled. Cytokines were started on day +1 posttransplant and continued to an absolute neutrophil count (ANC) of 5x10(9)/L for 3 days or 10x10(9)/L for 1 day. The median time to neutrophil engraftment (ANC >1.5x10(9)/L for 3 days or 5x10(9)/L for 1 day) was the same in both groups (12 days). No differences in platelet engraftment (11 versus 13 days), number of platelet transfusions (5 versus 4), percent with positive cultures for bacterial pathogens (23% versus 15%), days of fever (1 versus 2), deaths prior to engraftment (1 versus 1), or duration of hospital stay (19 versus 19 days) were seen between the pegfilgrastim and filgrastim groups, respectively. Using the average wholesale price for doses used in this trial, there was a per-patient savings of $961 for the pegfilgrastim group (P < .001). This phase III study failed to demonstrate a difference in time to neutrophil engraftment or any clinical sequelae between pegfilgrastim and filgrastim when given post-APBSCT, with pegfilgrastim achieving a cost savings over filgrastim.

Ladenstein R, Valteau-Couanet D, Brock P, et al. Randomized Trial of Prophylactic Granulocyte Colony-Stimulating Factor During Rapid COJEC Induction in Pediatric Patients With High-Risk Neuroblastoma: The European HR-NBL1/SIOPEN Study. *J Clin Oncol*. 2010; 28(21):3516–3524.
To reduce the incidence of febrile neutropenia during rapid COJEC (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide given in a rapid delivery schedule) induction. In the High-Risk Neuroblastoma-1 (HR-NBL1) trial, the International Society of Paediatric Oncology European Neuroblastoma Group (SIOPEN) randomly assigned patients to primary prophylactic (PP) versus symptom-triggered granulocyte colony-stimulating factor (GCSFs; filgrastim). From May 2002 to November 2005, 239 patients in 16 countries were randomly assigned to receive or not receive PPGCSFs. There were 144 boys with a median age of 3.1 years (range, 1 to 17 years) of whom 217 had International Neuroblastoma Staging System (INSS) stage 4 and 22 had stage 2 or 3 *MYCN*-amplified disease. The prophylactic arm received a single daily dose of 5 µg/kg GCSFs, starting after each of the eight COJEC chemotherapy cycles and stopping 24 hours before the next cycle. Chemotherapy was administered every 10 days regardless of hematologic recovery, provided that infection was controlled. The PPGCSFs arm had significantly fewer febrile neutropenic episodes ($P = .002$), days with fever ($P = .004$), hospital days ($P = .017$), and antibiotic days ($P = .001$). Reported Common Toxicity Criteria (CTC) graded toxicity was also significantly reduced: infections per cycle ($P = .002$), fever ($P < .001$), severe leucopenia ($P < .001$), neutropenia ($P < .001$), mucositis ($P = .002$), nausea/vomiting ($P = .045$), and constipation ($P = .008$). Severe weight loss was reduced significantly by 50% ($P = .013$). Protocol compliance with the rapid induction schedule was also significantly better in the PPGCSFs arm shown by shorter time to completion ($P = .005$). PPGCSFs did not adversely affect response rates or success of peripheral-blood stem-cell harvest.

Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. *Ann Oncol*. 2009; 21(7):1482–1485.

American Society of Clinical Oncology guidelines recommend the use of growth factor after high-dose chemotherapy (HDC) and peripheral blood stem cell (PBSC) support. This randomized trial aims to demonstrate the noninferiority of pegfilgrastim (PEG) compared with filgrastim (FIL) after HDC. Eighty patients were assigned to FIL at a daily dose of 5 μg/kg or a single fixed dose of PEG (6 mg) 1 day after PBSC. The primary end point was the duration of neutropenia both in terms of absolute neutrophil count (ANC) $<0.5 \times 10^9$/l and of days to reach an ANC $>0.5 \times 10^9$/l. The mean duration of neutropenia was 6 and 6.2 days and the mean time to reach an ANC $>0.5 \times 10^9$/l was 11.5 and 10.8 in the FIL and PEG group, respectively. No differences were observed in the mean time to reach an ANC $>1.0 \times 10^9$/l (12.2 versus 12.0 days) in the incidence of fever (62% versus 56%) and of documented infections (31% versus 25%). The mean duration of antibiotic therapy was 5.7 and 4.0 days in FIL and PEG group, respectively. PEG is not inferior to FIL in hematological reconstitution and represents an effective alternative after HDC and PBSC

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Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim Appears Equivalent to Daily Dosing of Filgrastim to Treat Neutropenia After Autologous Peripheral Blood Stem Cell Transplantation in Patients With Non-Hodgkin Lymphoma. *Clin Lymph Mye Leuk*. 2010; 10(3):186–191.

Filgrastim decreases the time to neutrophil recovery after autologous peripheral blood stem cell transplantation (PBSCT). We hypothesized that single-dose pegfilgrastim would mimic multiple daily doses of filgrastim, resulting in an equivalent shortening of post-PBSCT neutropenia. Patients who were eligible for PBSCT and aged ≥ 18 years were identified before high-dose chemotherapy, after the harvesting and cryopreservation of peripheral blood progenitor cells (ie, $> 2.5 \times 10^6$ CD34-positive cells/kg). Eligible patients received either standard carmustine/etoposide/cytarabine/melphalan (BEAM) or carmustine/etoposide/cytarabine/cyclophosphamide (BEAC) high-dose chemotherapy. Before high-dose chemotherapy, patients were randomly assigned to receive pegfilgrastim 6 mg on day 1 (arm A) or weight-based, dose-adjusted filgrastim beginning on day 1 (arm B) after transplantation until neutrophil engraftment. Results: One-hundred and one patients were enrolled between April 2003 and April 2007. Three patients were not treated. Demographics were well-balanced in terms of stage at diagnosis, Eastern Cooperative Oncology Group performance status, histology, and lines of previous therapy. Results (arm A/arm B) pertained to mean doses received (1.0/12.6), mean absolute neutrophil count recovery days (9.3/9.8), red blood cell transfusions (1.7/1.9), red blood cell transfusion units (3.1/3.8), platelet transfusions (3.1/2.8), positive blood culture rate (18%/29.2%), febrile neutropenia (FN; 18%/16.7%), and duration of FN (days; 7.1/6.9). Transplantation-related mortality and grade 3 or 4 adverse events were comparable between arms. Conclusion: Pegfilgrastim after PBSCT appears equivalent to multiple daily doses of filgrastim. This approach might be considered in lieu of filgrastim, thus obviating the need for multiple daily injections.

Talal AH, Liu R-C, Zeremski M, et al. Randomized trial comparing dose reduction and growth factor supplementation for management of hematological side effects in HIV/hepatitis C virus patients receiving pegylated-interferon and ribavirin. *J. Acquir. Immune Defic. Syndr.* 2011;58(3):261–26

Pegylated-interferon (PEG-IFN) and ribavirin (RBV), current standard treatment for hepatitis C virus (HCV) infection, are frequently associated with neutropenia and anemia, leading to high treatment discontinuation rates in HIV/HCV-coinfected patients. Our objective was to compare the effectiveness of intervening with hematologic growth factors versus dose reductions of standard HCV therapy for the management of treatment-induced hematologic disorders. Ninety-two HIV/HCV-coinfected, therapy-naive subjects received PEG-IFN alfa-2b 1.5 $\mu g \cdot kg^{-1} \cdot wk^{-1}$ and RBV 13 ± 2 $mg \cdot kg^{-1} \cdot d^{-1}$ for up to 48 weeks. Before treatment initiation, subjects were randomized to subsequently receive growth factors, recombinant human erythropoietin (rHuEPO) and/or granulocyte colony-stimulating factor, or dose reduction (RBV and/or PEG-IFN) for anemia and neutropenia management, respectively. We analyzed the ability of each management strategy to control anemia and neutropenia and the percentage of subjects who achieved a successful treatment outcome according to the different management strategies. During treatment, 43 subjects developed anemia (human erythropoietin, n = 24; dose reduction, n = 19), whereas 25 subjects developed neutropenia (granulocyte colony-stimulating factor, n = 10; dose reduction, n = 15). After the intervention, the increase in both hemoglobin and absolute neutrophil counts did not differ between the 2 side effect management strategies. Sustained response percentages were similar comparing anemic and neutropenic subjects regardless of management strategy (anemia: recombinant human erythropoietin, 29% versus dose reduction, 21%, P = 0.92; neutropenia: granulocyte colony-stimulating factor, 40% versus dose reduction, 20%, P = 0.46). Growth factor supplementation and dose reduction do not seem to differ as management strategies for anemia and neutropenia in HIV/HCV-coinfected individuals treated with PEG-IFN/RBV.