Clinical Policy Bulletin:
Hematopoietic Colony-Stimulating Factors (CSFs)

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Policy

Based on guidelines from the American Society of Clinical Oncology (Smith et al, 2006), Aetna considers granulocyte colony-stimulating factor (G-CSF; filgrastim [Neupogen], filgrastim-sndz [Zarxio], pegfilgrastim (Neulasta), or granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim [Leukine, Prokine]) for the prevention of febrile neutropenia (FN) medically necessary in adult and pediatric members with cancer for any of the following indications:

I. Primary prophylaxis

A. Individuals with non-myeloid malignancies receiving myelosuppressive chemotherapy that is expected to result in a 20 % or higher incidence of FN (see appendix); or

Note: In the absence of special circumstances, most commonly used regimens have risks of FN of less than 20 %. When available, alternative regimens offering equivalent efficacy, but not requiring CSF support, should be utilized (Smith et al, 2006).

B. Individuals receiving non-myelosuppressive chemotherapy who are considered to be at high risk for chemotherapy-induced FN infectious complications because of bone marrow compromise or co-morbidity, including any of the following (not an all-inclusive list):

1. Active infections or open wounds;
2. Age greater than 65 years;
3. Bone marrow involvement by tumor producing cytopenias;
4. Extensive prior treatment including large radiation ports;
5. Poor nutritional status;
6. Poor performance status
7. Previous episodes of FN;
8. Other serious co-morbidities.

II. Secondary prophylaxis for members who experienced a febrile neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received).

**Note:** Colony-stimulating factors should not be routinely used for afebrile neutropenia (Smith et al, 2006).

III. Therapeutic use in high-risk, febrile, neutropenic members who have any of the following prognostic factors that are predictive of clinical deterioration:

   A. Age greater than 65 years;
   B. Being hospitalized at the time of the development of fever;
   C. Hypotension;
   D. Invasive fungal infection;
   E. Multi-organ dysfunction;
   F. Pneumonia;
   G. Prolonged (greater than 10 days) and profound (absolute neutrophil count less than \(1 \times 10^9\)/L) neutropenia;
   H. Uncontrolled primary disease.

IV. To increase dose intensity chemotherapy regimens in settings where clinical research demonstrates that dose-intensive therapy produces improvement in disease control, when these therapies are expected to produce significant rates of FN (i.e., 20 % or higher incidence of FN).

V. Individuals with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy.

VI. Individuals with acute lymphoblastic leukemia (ALL) after completion of the first few days of chemotherapy of the initial induction or first post-remission course.

VII. Individuals receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.

VIII. Individuals with lymphoma aged 65 years and older treated with curative chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] or more aggressive regimens).

IX. Reduction in the duration of neutropenia and neutropenia-related infectious complications in members with non-myeloid malignancies undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplantation (BMT).

X. As adjunct to progenitor cell-transplantation to mobilize peripheral-blood progenitor-cells (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic transplant.

**Note:** Neulasta (pegfilgrastim) is not currently indicated for stem cell mobilization.
XI. Intermittent use in members with myelodysplastic syndromes who have less than 15% blasts in their bone marrow or are experiencing recurrent neutropenic infections.

XII. As treatment for radiation injury at doses of 3 to 10 Grays (Gy) or above.

Aetna considers granulocyte colony-stimulating factor (G-CSF; filgrastim [Neupogen], pegfilgrastim [Neulasta]; or granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim [Leukine, Prokine]) medically necessary for the prevention of febrile neutropenia in adult and pediatric members with either of the following non-oncologic indications:

Chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; or Individuals with advanced HIV infection and neutropenia (absolute neutrophil count less than 1 x 10^9/L) to allow scheduled dosing of myelosuppressive anti-retroviral medication (e.g., zidovudine and ganciclovir).

Aetna considers tbo-filgrastim [Granix, Neutroval]) for the prevention of febrile neutropenia (FN) medically necessary in adult and pediatric members with cancer for any of the following indications:

I. Primary prophylaxis
   A. Individuals with non-myeloid malignancies receiving myelosuppressive chemotherapy that is expected to result in a 20% or higher incidence of FN (see appendix); or
   B. Individuals receiving non-myelosuppressive chemotherapy who are considered to be at high risk for chemotherapy-induced FN infectious complications because of bone marrow compromise or co-morbidity, including any of the following (not an all-inclusive list):
      1. Active infections or open wounds;
      2. Age greater than 65 years;
      3. Bone marrow involvement by tumor producing cytopenias;
      4. Extensive prior treatment including large radiation ports;
      5. Poor nutritional status;
      6. Poor performance status
      7. Previous episodes of FN;
      8. Other serious co-morbidities.

II. Secondary prophylaxis for members who experienced a febrile neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received).

III. Therapeutic use in high-risk, febrile, neutropenic members who have any of the following prognostic factors that are predictive of clinical deterioration:
   A. Age greater than 65 years;
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B. Being hospitalized at the time of the development of fever;
C. Hypotension;
D. Invasive fungal infection;
E. Multi-organ dysfunction;
F. Pneumonia;
G. Prolonged (greater than 10 days) and profound (absolute neutrophil count less than 1 x 10^9/L) neutropenia;
H. Uncontrolled primary disease.

IV. To increase dose intensity chemotherapy regimens in settings where clinical research demonstrates that dose-intensive therapy produces improvement in disease control, when these therapies are expected to produce significant rates of FN (i.e., 20 % or higher incidence of FN).

V. Individuals with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy.

VI. Reduction in the duration of neutropenia and neutropenia-related infectious complications in members with non-myeloid malignancies undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplantation (BMT).

VII. As adjunct to progenitor cell-transplantation to mobilize peripheral-blood progenitor-cells (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic transplant.

Aetna considers tbo-filgrastim [Granix, Neutroval] medically necessary for the prevention of febrile neutropenia in adult and pediatric members with either of the following non-oncologic indications:

Chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; or
Individuals with advanced HIV infection and neutropenia (absolute neutrophil count less than 1 x 10^9/L) to allow scheduled dosing of myelosuppressive anti-retroviral medication (e.g., zidovudine and ganciclovir).

Aetna considers granulocyte colony-stimulating factor or granulocyte macrophage colony stimulating factor experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established, including any of the following:

Chemosensitization of myeloid leukemias;
Continued use if no response is seen within 28 to 42 days (members who have failed to respond within this time frame are considered non-responders);
Neutropenic members who are afebrile;
Post allogeneic transplant support in myeloid malignancies;
Prophylactic reduction of sepsis and improvement of survival in pre-term neonates;
Routine use in most chemotherapy regimens as prophylaxis;
Treatment of amyotrophic lateral sclerosis;
Treatment of antiviral-associated neutropenia in persons with hepatitis C; Treatment of aplastic anemia; Treatment of Asherman's syndrome (amenorrhea due to intrauterine adhesions); Treatment of cancer-related fatigue; Treatment of Crohn's disease; Treatment of diabetic foot infections; Treatment of Felty syndrome; Treatment of interferon-induced neutropenia; Treatment of ischemic heart disease; Treatment of melanoma; Treatment of myocardial infarction; Treatment of neutropenia in recipients of kidney transplantation; Treatment of peripheral artery disease; Treatment of pneumonia (other than febrile, neutropenic persons, as noted above); Treatment of prostate cancer; Treatment of spinal cord injury; Treatment of stroke; Use as adjunctive therapy to antibiotics in members with uncomplicated febrile neutropenia, which is defined as febrile neutropenia not meeting the high-risk criteria outlined above; Use either before and/or concurrently with chemotherapy for "priming" effects; Use in members receiving concomitant chemotherapy and radiation therapy; Use in women undergoing assisted reproduction technologies; Use to increase the dose-intensity or schedule of cytotoxic chemotherapy beyond established dosage range for these regimens.

Background

This policy is adapted from guidelines from the American Society for Clinical Oncology (ASCO) (Smith et al, 2006).

Standard practice in protecting against chemotherapy-associated infection has been chemotherapy dose modification or dose delay, administration of progenitor-cell support, or selective use of prophylactic antibiotics. Chemotherapy associated neutropenic fever or infection has customarily involved treatment with intravenous antibiotics, usually accompanied by hospitalization. The hematopoietic colony-stimulating factors (CSFs) have been introduced into clinical practice as additional supportive measures that can reduce the likelihood of neutropenic complications due to chemotherapy.

Colony-stimulating factors are recommended in some situations, e.g., to reduce the likelihood of febrile neutropenia (FN) when the expected incidence is greater than 20 %; after documented FN in a prior chemotherapy cycle to avoid infectious complications and maintain dose-intensity in subsequent treatment cycles when chemotherapy dose-reduction is not appropriate; and after high-dose chemotherapy with autologous progenitor-cell transplantation. Colony-stimulating factors are also effective in the mobilization of peripheral-blood progenitor cells. Therapeutic initiation of CSFs in addition to antibiotics at the onset of FN should be reserved for patients at high risk for septic complications. Use of CSFs in patients with myelodysplastic syndromes may be reasonable if they are experiencing neutropenic infections. Administration of CSFs after initial chemotherapy for
acute myeloid leukemia does not appear to be detrimental, but clinical benefit has been variable and caution is advised. Available data support use of CSFs in pediatric cancer patients similar to that recommended for adult patients. Colony-stimulating factors should not be used concurrently with chemotherapy and radiation, or to support increasing dose-dense chemotherapy regimens.

In adult cancer patients receiving myelosuppressive chemotherapy, the Food and Drug Administration (FDA)-approved labeling recommends a starting dose of granulocyte-CSF (filgrastim, Neupogen) of 5 micrograms per kilogram per day (mcg/kg/day). Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir.

In adult cancer patients receiving bone marrow transplant, the recommended dose of Neupogen is 10 mcg/kg/day given as an intravenous infusion of 4 or 24 hours, or as a continuous 24-hour subcutaneous infusion. The first dose should be administered at least 24 hours after cytotoxic chemotherapy or after bone marrow infusion. The recommended dose of Neupogen for the mobilization of peripheral blood progenitor cells is 10 mcg/kg/day subcutaneously, either as a bolus or a continuous infusion, given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. The recommended daily starting dose for congenital neutropenia is 6 mcg/kg twice-daily subcutaneously every day and for idiopathic or cyclic neutropenia is 5 mcg/kg as a single injection subcutaneously every day.

The recommended dosage for granulocyte-macrophage-CSF (sargramostim, Leukine) is 250 mcg/m2/day for all clinical settings.

Other than for peripheral blood progenitor cell re-infusion, CSFs should be administered subcutaneously or intravenously no earlier than 24 hours and preferably between 24 and 72 hours after the administration of cytotoxic chemotherapy to provide optimal neutrophil recovery. Therapy should be discontinued if the absolute neutrophil count surpasses 10,000/mm3 after the expected chemotherapy-induced nadir. Starting CSFs up to 5 days after peripheral blood progenitor cell re-infusion is reasonable based on available clinical data.

Neulasta (pegfilgrastim), a long acting version of Neupogen (filgrastim), is administered once per chemotherapy cycle. It is approved by the FDA to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of FN. Neulasta is not labeled for use in myeloid malignancies -- leukemias and lymphomas - because there is concern that it may stimulate the tumor cells to grow and it is not currently indicated for stem cell mobilization.

According to the FDA-approved labeling, the recommended dose of Neulasta is a single subcutaneous injection of 6 mg, administered once per chemotherapy cycle. According to the labeling, Neulasta should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

NCCN guidelines on myeloid growth factors state that administration of pegfilgrastim next day or up to 3 to 4 days following chemotherapy is preferred; however the panel agreed that same-day administration of pegfilgrastim may be considered under certain circumstances, defined as administration of pegfilgrastim on the day during which patients receive chemotherapy. NCCN panelists stated that same-day administration is done for
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...logical reasons and to minimize burdens on long-distance patients. NCCN guidelines note that clinical trials both in support of and against same-day pegfilgrastim have been published. The guidelines explain that the original rationale for not giving same-day CSF was the potential for increased neutropenia resulting from CSF stimulation of myeloid progenitors at the time of cytotoxic chemotherapy. The guidelines cited a direct comparison (citing Kaufman, et al.), where pegfilgrastim was administered either same-day or next-day in women with breast cancer receiving chemotherapy. Febrile neutropenia was observed in 33 percent of patients treated in the same-day group compared with only 11 percent of patients in the next-day group. The NCCN guidelines observed that a similar trend was seen in a prospective randomized double-blind trial of patients receiving chemotherapy for NHL where same-day pegfilgrastim was associated with enhanced myelosuppression and no reduction of leukopenia was seen. However, despite longer duration of grade 4 neutropenia in the same-day group, there was no increase in the overall incidence of neutropenia and the increased duration did not meet the non-inferiority margin. The guidelines noted that, while this study recommends administration of pegfilgrastim 24 hours after chemotherapy, it was acknowledged that same-day administration may be an acceptable alternative for some patients.

NCCN guidelines also described a retrospective review by Vance, et al. of same-day pegfilgrastim in patients with breast cancer receiving chemotherapy and no increased neutropenia was observed. The guidelines also identified a retrospective study of 159 patients with a variety of tumor types and chemotherapy regimens showing a similar incidence of myelosuppressive adverse events when comparing the two groups. A double-blind phase II study in patients with non-small cell lung cancer treated with chemotherapy showed no increase in neutropenia nor any adverse events in patients receiving same-day pegfilgrastim compared to patients receiving next-day pegfilgrastim treatment. The benefit of same-day pegfilgrastim was also observed in patients with non-small cell lung cancer treated with weekly chemotherapy regimens. Same day pegfilgrastim in these patients was shown to be beneficial not only from a safety perspective but also from a logistical one where next-day pegfilgrastim would have compromised the weekly chemotherapy schedule. Anotehr study in patients with lung cancer showed an unexpected low rate of severe neutropenia (only 2 patients per group) suggesting that same-day filgrastim is a reasonable option. More recent retrospective studies in patients with gynecologic malignancies demonstrated the safety and efficacy of pegfilgrastim administered within 24 hours of chemotherapy.

Micromedex DrugDex compendium states that the use of pegfilgrastim in the period between 14 days before and 24 hours after chemotherapy is not recommended. It states that pegfilgrastim administered once on the same day as chemotherapy was shown to be noninferior to pegfilgrastim administered once 24 hours after chemotherapy for the duration of grade 4 neutropenia after the first cycle of chemotherapy in patients with breast cancer and non-Hodgkin lymphoma; however, the duration of grade 4 neutropenia was longer and the incidence of febrile neutropenia was higher with same-day compared with next-day administration. The Compendium cited a study by Burris, et al. that compared data on severe (grade 4) neutropenia duration and febrile neutropenia incidence in patients receiving chemotherapy with pegfilgrastim administered the same day or 24 hours after chemotherapy. Burris, et al. noted that these were similar, randomized, double-blind phase II noninferiority studies of patients with lymphoma or non-small-cell lung (NSCLC), breast, or ovarian cancer. Each study was analyzed separately. The primary end point in each study was cycle-1 severe neutropenia duration. Approximately 90 patients per study were to be randomly assigned at a ratio of 1:1 to receive pegfilgrastim 6 mg once
per cycle on the day of chemotherapy or the day after (with placebo on the alternate day). The authors found that, in four studies, 272 patients received chemotherapy and one or more doses of pegfilgrastim (133 same day, 139 next day). Three studies (breast, lymphoma, NSCLC) enrolled an adequate number of patients for analysis. However, in the NSCLC study, the neutropenic rate was lower than expected (only two patients per arm experienced grade 4 neutropenia). In the breast cancer study, the mean cycle-1 severe neutropenia duration was 1.2 days (95% confidence limit [CL], 0.7 to 1.6) longer in the same-day compared with the next-day group (mean, 2.6 v 1.4 days). In the lymphoma study, the mean cycle-1 severe neutropenia duration was 0.9 days (95% CL, 0.3 to 1.4) longer in the same-day compared with the next-day group (mean, 2.1 v 1.2 days). In the breast and lymphoma studies, the absolute neutrophil count profile for same-day patients was earlier, deeper, and longer compared with that for next-day patients, although the results indicate that same-day administration was statistically noninferior to next-day administration according to neutropenia duration. The authors concluded that, for or patients receiving pegfilgrastim with chemotherapy, pegfilgrastim administered 24 hours after chemotherapy completion is recommended.

An UpToDate review of the use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia (Larson, 2014) stated: “Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, growth factors should be discontinued several days before the next chemotherapy treatment and they should not be given on the same day as chemotherapy. Experience from clinical trials indicates that myelosuppression is more profound if the myeloid growth factors were given immediately prior to or on the same day as the chemotherapy. For the same reason, growth factors should not be given concurrently with radiation therapy directed at portals containing active marrow.”

Hematological side effects (e.g., anemia, neutropenia, and thrombocytopenia) of combination therapy with pegylated (PEG)-interferon alfa and ribavirin are commonly encountered during antiviral therapy for chronic hepatitis C (HCV) (Collantes and Younossi, 2005). An important consequence of these side effects is dose modification of PEG-interferon alfa, ribavirin, or both. The FDA-approved product labeling of both peginterferon preparations (alfa-2a and alfa-2b) recommend dose reduction for patients with neutrophils counts less than 750 cells/mm3 and drug discontinuation for those with counts less than 500 cells/mm3. However, there has been concern that such dose modifications will diminish the effectiveness of optimal treatment regimen for HCV and may have a negative impact on sustained virological response.

Collantes and Younossi (2005) note that the clinical implications of neutropenia or thrombocytopenia are less clear than for anemia; nevertheless, severe infection and bleeding are uncommon. Dose adjustments effectively treat these hematological side effects, but the resulting sub-optimal dosing and potential impact on virological response are major concerns. Recent attempts to maximize adherence to the optimal treatment regimen have used hematopoietic growth factors rather than dose adjustment to treat side effects. Research on growth factor support has focused on anemia and neutropenia. Erythropoietin and darbepoetin alfa are erythropoietic growth factors that effectively increase hemoglobin while maintaining the optimal ribavirin dose and improving patients’ quality of life (see CPB 0195 - Erythropoiesis Stimulating Agents).

Investigators have examined the potential for adjunctive use of the granulocyte colony stimulating factor (G-CSF) filgrastim to improve clinical outcomes in persons with chronic
hepatitis C. Early clinical studies found that routine co-administration of filgrastim failed to significantly enhance the sustained virologic response to interferon-based therapies in hepatitis C (Gronbaek et al, 2002; Van Thiel et al, 1995). Clinical studies are needed to assess the effectiveness of G-CSF to treat chemotherapy induced neutropenia in hepatitis C.

Collantes and Younossi (2005) concluded that, although filgrastim shows tremendous promise for managing hematological side effects of combination therapy for HCV, and potentially enhancing adherence, further research is needed to clarify the safety, effectiveness, and cost-effectiveness of growth factors in the management of patients with chronic HCV. Ong and Younossi (2004) reached similar conclusions, noting that the impact of growth factors on sustained virological response and their cost-effectiveness in patients with chronic HCV need further assessment.

The Canadian Agency for Drugs and Technologies in Health (Dryden et al, 2008) released a report on G-CSF for antiviral-associated neutropenia. A systematic review was used to evaluate the effect of treatment with G-CSF compared with that of interferon dose reduction to control neutropenia. It was not superior to interferon dose reduction. While G-CSF may enable patients to stay on or resume optimal antiviral therapy, the evidence is weak. The mild adverse effects respond to simple treatments that alleviate symptoms. The report concluded that it is unclear if the use of G-CSF compared with dose reduction improves sustained virological response in patients with hepatitis C and neutropenia.

Early research is examining the potential for G-CSF to enhance myocardial function in myocardial infarction (MI). In a prospective, randomized, double-blinded, placebo-controlled phase II clinical trial, Engelmann et al (2006) compared the effects of G-CSF on the improvement of MI in patients undergoing delayed percutaneous coronary intervention (PCI) for ST-segment elevation MI (STEMI). A total of 44 patients with late re-vascularized subacute STEMI were treated either with G-CSF or placebo over 5 days after successful PCI. Primary end points were change of global and regional MI from baseline (1 week after PCI) to 3 months after PCI evaluated by magnetic resonance imaging (MRI). Secondary end points consisted of characterization of mobilized stem cell populations, assessment of safety parameters up to 12 months including 6-month angiography, as well as myocardial perfusion evaluated by MRI. Global myocardial function from baseline (1 week after PCI) to 3 months improved in both groups, but G-CSF was not superior to placebo. A slight but non-significant improvement of regional function occurred in both groups. Granulocyte-CSF resulted in mobilization of endothelial progenitor cell populations and was well-tolerated with a similar rate of target lesion re-vascularization from in-stent re-stenosis. In both groups major adverse cardiovascular events occurred in a comparable frequency; G-CSF resulted in significant improvement of myocardial perfusion 1 week and 1 month after PCI. The authors concluded that G-CSF treatment after PCI in subacute STEMI is feasible and relatively safe. However, patients do not benefit from G-CSF when PCI is performed late. They noted that as a result of its phase II character, this trial is limited by its small sample size. These investigators stated that further research should focus on immediate administration of G-CSF in early re-vascularized MI and on larger multi-center studies examining clinical outcomes.

In a meta-analysis, Abdel-Latif and colleagues (2008) examined the effects of G-CSF therapy for cardiac repair after acute MI. These investigators searched Medline, Embase, Science Citation Index, CINAHL, and the Cochrane Central database of controlled clinical trials for randomized controlled trials of G-CSF therapy in patients with acute MI. They
conducted a fixed-effects meta-analysis across 8 eligible studies (n = 385 patients). Compared with controls, G-CSF therapy increased LV ejection fraction (EF) by 1.09 %, increased LV scar size by 0.22 %, decreased LV end-diastolic volume by 4.26 ml, and decreased LV end-systolic volume by 2.50 ml. None of these effects was statistically significant. The risk of death, recurrent MI, and in-stent re-stenosis was similar in G-CSF-treated patients and controls. Subgroup analysis revealed a modest but statistically significant increase in EF (4.73 %, p < 0.0001) with G-CSF therapy in studies that enrolled patients with mean EF less than 50 % at baseline. Subgroup analysis also showed a significant increase in EF (4.65 %, p < 0.0001) when G-CSF was administered relatively early (less than or equal to 37 hours) after the acute event. The authors concluded that G-CSF therapy in unselected patients with acute MI appears safe but does not provide an overall benefit. Subgroup analyses suggested that G-CSF therapy may be salutary in acute MI patients with LV dysfunction and when started early. They stated that larger randomized studies are needed to evaluate the potential benefits of early G-CSF therapy in acute MI patients with LV dysfunction. This is in agreement with the findings of Zohlnhöfer et al (2008) who reported that available evidence does not support a beneficial effect of G-CSF in patients with acute MI after re-perfusion.

Beohar et al (2010) stated that cytokine therapy including G-CSF and granulocyte-macrophage colony stimulating factor (GM-CSF) promises to provide a non-invasive treatment option for ischemic heart disease. Cytokines are thought to influence angiogenesis directly via effects on endothelial cells or indirectly through progenitor cell-based mechanisms or by activating the expression of other angiogenic agents. Several cytokines mobilize progenitor cells from the bone marrow or are involved in the homing of mobilized cells to ischemic tissue. The recruited cells contribute to myocardial regeneration both as a structural component of the regenerating tissue and by secreting angiogenic or anti-apoptotic factors, including cytokines. To date, randomized controlled trials (RCTs) have not reproduced the efficacy observed in pre-clinical and small-scale clinical investigations. Nevertheless, the list of promising cytokines continues to grow, and combinations of cytokines, with or without concurrent progenitor cell therapy, warrant further investigation. In particular, the authors stated that the mechanism of action and potential inflammatory sequelae associated with GM-CSF must be better understood and controlled before larger human trials can be considered.

A Cochrane review found insufficient evidence to support the use of G-CSF for treating stroke (Bath and Sprigg, 2006). The investigators found that G-CSF was associated with a non-significant reduction in combined death and dependency in 2 small trials (n = 46 subjects), although there was substantial heterogeneity in this result. These investigators concluded that there was insufficient evidence to support the use of G-CSF in the treatment of patients with recurrent stroke.

In a Cochrane review, Cheng et al (2007) examined the role of G-CSF as an adjunct to antibiotics in the treatment of pneumonia in non-neutropenic adults. The investigators found that, when, combined with antibiotics, G-CSF appears to be a safe treatment for people with pneumonia, but it does not appear to reduce mortality. The authors concluded that currently there is no evidence to support the routine use of G-CSF in the treatment of pneumonia. They noted that studies in which G-CSF is administered prophylactically or earlier in therapy may be of interest.

Felty syndrome (FS) is a rare but severe subset of sero-positive rheumatoid arthritis (RA) complicated by granulocytopenia and splenomegaly; occurring in less than 1 % of patients...
with RA. The granulocytopenia in FS may improve when RA is treated with second-line medications such as gold, methotrexate, and corticosteroids. Moreover, G-CSF has been studied in the treatment of patients with FS.

Stanworth and co-workers (1998) prospectively monitored the use of G-CSF in 8 FS patients with recurrent infections or who required joint surgery. Significant side effects were documented in 5, including nausea, malaise, generalized joint pains, and in 1 patient, a vasculitic skin rash. In 2 patients treatment had to be stopped, and in these cases G-CSF had been started at full vial dosage (300 micrograms/ml filgrastim or 263 micrograms/ml lenograstim) alternate days or daily. Treatment with G-CSF was continued in 3 patients by re-starting at a lower dose, and changing the proprietary formulation. Treatment with G-CSF increased the neutrophil count, decreased severe infection, and allowed surgery to be performed. A combined clinical and laboratory index suggested that long-term treatment (up to 3.5 years) did not exacerbate the arthritis. Once on established treatment, it may be possible to use smaller weekly doses of G-CSF to maintain the same clinical benefit. One of the 3 patients whose FS was associated with a large granular T-cell lymphocytosis showed a reduction in this subset of lymphocytes during G-CSF treatment.

Balint and Balint (2004) noted that over 95 % of FS patients are positive for rheumatoid factor, 47 to 100 % are positive for anti-nuclear antibody (ANA), and 78 % of patients have the HLA-DR4*0401 antigen. Some 30 % of FS patients have large granular lymphocyte expansion. Large granular lymphocyte expansion associated with uncomplicated RA is immunogenetically and phenotypically very similar to but clinically different from FS. Neutropenia of FS can be effectively treated with disease-modifying anti-rheumatic drugs, the widest experience being with methotrexate. Furthermore, results of treatment with G-CSF are encouraging. Splenectomy results in immediate improvement of neutropenia in 80 % of the patients, but the rate of infection decreases to a lesser degree.

In a phase I study, Sato et al (2008) examined the feasibility and safety of immuno-embolization with GM-CSF; sargramostim for malignant liver tumors, predominantly hepatic metastases from patients with primary uveal melanoma. A total of 39 patients with surgically unresectable malignant liver tumors, including 34 patients with primary uveal melanoma, were enrolled. Hepatic artery embolization accompanied an infusion of dose-escalated GM-CSF (25 to 2,000 microg) given every 4 weeks. Primary end points included dose-limiting toxicity and maximum tolerated dose (MTD). Patients who completed 2 cycles of treatments were monitored for hepatic anti-tumor response. Survival rates of patients were also monitored. Maximum tolerated dose was not reached up to the dose level of 2,000 microg, and there were no treatment-related deaths. A total of 31 assessable patients with uveal melanoma demonstrated 2 complete responses, 8 partial responses, and 10 occurrences of stable disease in their hepatic metastases. The median overall survival of intent-to-treat patients who had metastatic uveal melanoma was 14.4 months. Multi-variate analyses indicated that female sex, high doses of GM-CSF (greater than or equal to 1,500 microg), and regression of hepatic metastases (complete and partial responses) were correlated to longer overall survival. Moreover, high doses of GM-CSF were associated with prolonged progression-free survival in extra-hepatic sites. The authors concluded that immuno-embolization with GM-CSF is safe and feasible in patients with hepatic metastasis from primary uveal melanoma. Encouraging preliminary efficacy and safety results warrant additional clinical study in metastatic uveal melanoma.
Daud et al (2008) conducted a prospective trial in patients with high-risk (stage III B/C, IV), resected melanoma, with GM-CSF 125 microg/m(2)/d administered for 14 days every 28 days. Patients underwent clinical restaging every 4 cycles, with dendritic cells (DCs) analysis performed at baseline and at 2, 4, 8, and 12 weeks. Of 42 patients enrolled, 39 were assessable for clinical outcome and DC analysis. Median overall survival was 65 months (95 % confidence interval [CI]: 43 to 67 months) and recurrence-free survival was 5.6 months (95 % CI: 3 to 11 months). Treatment with GM-CSF caused an increase in mature DCs, first identified after 2 weeks of treatment, normalizing by 4 weeks. Patients with decreased DCs at baseline had significant increases in DC number and function compared with those with “normal” parameters at baseline. No change was observed in the number of myeloid-derived suppressor cells (MDSCs). Early recurrence (less than 90 days) correlated with a decreased effect of GM-CSF on host DCs, compared with late or no (evidence of) recurrence. The authors concluded that GM-CSF treatment was associated with a transient increase in mature DCs, but not MDSCs. Greater increase of DCs was associated with remission or delayed recurrence. The prolonged overall survival observed warrants further exploration.

In a phase I study, Lutzky et al (2009) evaluated the safety and tolerability of adjuvant treatment with subcutaneous GM-CSF administered in combination with escalating doses of thalidomide in patients with surgically resected stage II (T4), III, or IV melanoma at high risk for recurrence. Adjuvant treatment included GM-CSF 125 microg/m2 subcutaneously for 14 days and thalidomide at an initial dose of 50 mg/d, escalated in cohorts of 3 to 6 patients each to a maximum of 400 mg/day followed by 14 days of rest. Treatment was continued for up to 1 year in the absence of disease progression. Of 19 patients treated, the most common toxicities were grade 1/2 constipation (68 %), fatigue (58 %), neuropathy (42 %), bone and joint pain (37 %), and dyspnea, dizziness, injection site skin reaction, and somnolence (32 % each). Thrombotic events in 3 of 19 patients (16 %), including 1 treatment-related death, were the most serious adverse events and were thought to be due to thalidomide. With a median follow-up of 945 days (2.6 years), 8 (42 %) patients were alive, including 1 with disease and 7 without evidence of disease. Treatment with GM-CSF plus thalidomide for patients with resected high-risk melanoma was associated with a high incidence of thrombotic events. Because life-threatening events are unacceptable in the adjuvant setting, up-front anti-thrombotic prophylaxis will be necessary for further evaluation of GM-CSF plus thalidomide as a viable regimen in this patient group.

In a phase I-II study, Urba and colleagues (2008) evaluated the safety, clinical activity and immunogenicity of an immunotherapy developed from human prostate cancer cell lines (PC-3 and LNCaP) modified to secrete GM-CSF. Patients with non-castrate prostate cancer with biochemical (prostate specific antigen) recurrence following prostatectomy or radiation therapy and no radiological evidence of metastasis were enrolled in the study (n = 19). They were injected with an initial dose of 5 x 10(8) cells followed by 12 bi-weekly administrations of 1 x 10(8) cells. The adverse event profile, prostate specific antigen (PSA) response, changes in PSA kinetics and immunogenicity were assessed. Immunotherapy was well-tolerated with no serious treatment related adverse events and no autoimmune responses. A negative deflection in PSA slope was observed in 84 % of patients after treatment with a significant increase in median PSA doubling time from 28.7 weeks before treatment to 57.1 weeks after treatment (p = 0.0095). Median time to PSA progression was 9.7 months. Immunoblot analysis of patient serum demonstrated new or enhanced production of PC-3 or LNCaP reactive antibodies in 15 of 19 (79 %) patients after immunotherapy. Induction of antibody responses reactive against PC-3 in general,
In an open-label, multi-center, dose-escalation study, Higano and associates (2008) assessed multiple dose levels of immunotherapy in patients with metastatic hormone-refractory prostate cancer (HRPC). The immunotherapy, based on the GVAX (prostate cancer vaccine) platform, consisted of 2 allogeneic prostate-carcinoma cell lines modified to secrete GM-CSF. Dose levels ranged from 100 x 10⁶ cells q28d x 6 to 500 x 10⁶ cells prime/300 x 10⁶ cells boost q14d x 11. Endpoints included safety, immunogenicity, overall survival, radiologic response, PSA kinetics, and serum GM-CSF pharmacokinetics. A total of 80 men, median age of 69 years (range of 49 to 90 years), were treated. The most common adverse effect was injection-site erythema. Overall, the immunotherapy was well-tolerated. A maximal tolerated dose was not established. The median survival time was 35.0 months in the high-dose group, 20.0 months in the mid-dose, group, and 23.1 months in the low-dose group. Prostate specific antigen stabilization occurred in 15 (19%) patients, and a greater than 50% decline in PSA was seen in 1 patient. The proportion of patients who generated an antibody response to 1 or both cell lines increased with dose and included 10 of 23 (43%) in the low-dose group, 13 of 18 (72%) in the mid-dose group, and 16 of 18 (89%) in the high-dose group (p = 0.002; Cochran-Armitage trend test). The authors concluded that this immunotherapy was well-tolerated; immunogenicity and overall survival varied by dose. They also noted that 2 phase III clinical trials in patients with metastatic HRPC are underway.

Si et al (2009) examined the effects of combined cryoablation and GM-CSF treatment for metastatic hormone refractory prostate cancer. A total of 12 patients with metastatic hormone refractory prostate cancer were treated by combining cryoablation and GM-CSF administration. Besides PSA measurements, peripheral blood mononuclear cells were also obtained; the frequency of tumor-specific T cells was tested ex vivo in an interferon-gamma enzyme-linked immunospot assay after stimulating with autologous prostate cancer-derived protein lysates. To assess cytolytic activity, T cells were co-incubated with LNCaP or renal cancer cells (GRC-1), and release of cytosolic adenylate kinase was measured by a luciferase assay. The median PSA decline percentage was 69.4% (range of 30.5% to 92.5%) and the median time to the nadir PSA was 4 months after therapy (range of 3 to 6 months). The median time to disease progress was 18 months, and 1 patient obtained a 92.5% PSA decline and a greater than 50% reduction of lung disease and survived 31 months. Four or 8 weeks after treatment, the tumor-specific T-cell responses were increased in peripheral blood mononuclear cell. The cytolytic activity against LNCaP was also increased significantly whereas no response was found against GRC-1. It seemed that there was no direct correlation between the degree of T-cell response and decline in PSA. The authors suggested that combined cryoablation with GM-CSF treatment may be an alternative approach for metastatic hormone refractory prostate cancer.

Amato and colleagues (2009) evaluated the effectiveness of GM-CSF in combination with thalidomide on PSA reduction in hormone-naïve prostate carcinoma (HNPC) patients with rising PSA levels after definitive local treatment. Patients (n = 21) with evidence of progression demonstrated by 3 consecutive rises in PSA and no evidence of radiographic...
involvement were treated on a chronic dosing schedule with GM-CSF. They received 250 microg/m2 (maximum 500 microg) 3 times a week by subcutaneous injection, with injections at least 24 hours apart. Thalidomide administration began concurrently with an initial dose of 100 mg daily for 7 consecutive days. During week 2 to 4, the dose was escalated every 7 days by 100 mg per individual tolerance to a maximum of 400 mg. The maximum tolerated dose of thalidomide was continued without interruption. Prostate specific antigen, testosterone, and routine laboratory parameters were measured every 6 weeks. One patient was not evaluable because of non-compliance. For the 20 evaluable patients, baseline PSA levels ranged from 1.3 to 61.0 ng/ml. A total of 19 patients left the study at 3.0 to 33.3 months, secondary to individual tolerance, progressive disease, or development of a second primary tumor. One patient continues to receive therapy at 33.8 months. Two patients did not respond to the therapy. For the 18 patients who did respond, the median reduction in PSA level was 59 % (range of 26 % to 89 %), and the median duration of response was 11 months (range of 4.5 to 36 months). Grades 1-2 toxicity included peripheral neuropathy, fatigue, skin rash, and constipation. One patient had deep-vein thrombosis/pulmonary embolism. The authors concluded that GM-CSF plus thalidomide can be administered successfully with encouraging anti-tumor activity and reversible toxicity. This may represent an alternative to hormonal therapy.

Battiwalla and McCarthy (2009) noted that the cytokine G-CSF stimulates myeloid progenitors and is routinely used to accelerate neutrophil recovery in the treatment of hematological malignancy and blood or marrow transplantation. Despite significant reductions in the frequency and duration of FN episodes, infections and the length of hospitalization, filgrastim has never been conclusively proven to produce a survival benefit in allogeneic hematopoietic stem cell transplantation (HSCT) and is considered a supportive measure. These investigators analyzed the conflicting evidence and appraised the utility of G-CSF in allogeneic HSCT. They concluded that G-CSF administration following allogeneic HSCT needs to take into consideration the impact on immune reconstitution, risk of leukemic progression in patients with chromosome 7 abnormalities and the absence of proven benefit in patients receiving marrow or peripheral blood progenitors as the stem cell source. The authors also noted that although there is conflicting evidence whether the administration of G-CSF post allogeneic transplant worsens survival, there is no apparent benefit.

In a single-blind, multi-center, RCT, Carr and associates (2009) examined if GM-CSF administered as prophylaxis to pre-term neonates at high-risk of neutropenia would reduce sepsis, mortality, and morbidity. A total of 280 neonates of below or equal to 31 weeks' gestation and below the 10th centile for birth weight were randomized within 72 hrs of birth to receive GM-CSF 10 microg/kg per day subcutaneously for 5 days or standard management. From recruitment to day 28, a detailed daily clinical record form was completed by the treating clinicians. Primary outcome was sepsis-free survival to 14 days from trial entry. Analysis was by intention-to-treat. Neutrophil counts after trial entry rose significantly more rapidly in infants treated with GM-CSF than in control infants during the first 11 days (difference between neutrophil count slopes 0.34 x 10(9)/L/day; 95 % CI: 0.12 to 0.56). There was no significant difference in sepsis-free survival for all infants (93 of 139 treated infants, 105 of 141 control infants; difference -8 %, 95 % CI: -18 to 3). A meta-analysis of this trial and previous published prophylactic trials showed no survival benefit. The authors concluded that early post-natal prophylactic GM-CSF corrects neutropenia but does not reduce sepsis or improve survival and short-term outcomes in extremely pre-term neonates.
In a meta-analysis, Bo et al (2011) examined the effects of G-CSF or GM-CSF therapy in non-neutropenic patients with sepsis. A systematic literature search of Medline, Embase and Cochrane Central Register of Controlled Trials was conducted using specific search terms. A manual review of references was also performed. Eligible studies were RCTs that compared G-CSF or GM-CSF therapy with placebo for the treatment of sepsis in adults. Main outcome measures were all-cause mortality at 14 days and 28 days after initiation of G-CSF or GM-CSF therapy, in-hospital mortality, reversal rate from infection, and adverse events. A total of 12 RCTs with 2,380 patients were identified. In regard to 14-day mortality, a total of 9 death events occurred among 71 patients (12.7 %) in the treatment group compared with 13 events among 67 patients (19.4 %) in the placebo groups. Meta-analysis showed there was no significant difference in 28-day mortality when G-CSF or GM-CSF were compared with placebo (relative risks (RR) = 0.93, 95 % CI: 0.79 to 1.11, p = 0.44; p for heterogeneity = 0.31, I2 = 15 %). Compared with placebo, G-CSF or GM-CSF therapy did not significantly reduce in-hospital mortality (RR = 0.97, 95 % CI: 0.69 to 1.36, p = 0.86; p for heterogeneity = 0.80, I2 = 0 %). However, G-CSF or GM-CSF therapy significantly increased the reversal rate from infection (RR = 1.34, 95 % CI: 1.11 to 1.62, p = 0.002; p for heterogeneity = 0.47, I2 = 0 %). No significant difference was observed in adverse events between groups (RR = 0.93, 95 % CI: 0.70 to 1.23, p = 0.62; p for heterogeneity = 0.03, I2 = 58 %). Sensitivity analysis by excluding one trial did not significantly change the results of adverse events (RR = 1.05, 95 % CI: 0.84 to 1.32, p = 0.44; p for heterogeneity = 0.17, I2 = 36 %). The authors concluded that there is no current evidence supporting the routine use of G-CSF or GM-CSF in patients with sepsis. They stated that large prospective multi-center clinical trials investigating monocytic HLA-DR (mHLA-DR)-guided G-CSF or GM-CSF therapy in patients with sepsis-associated immunosuppression are needed.

Granulocyte-CSF is used to mobilize CD34+ hematopoietic stem cells from the bone marrow to the peripheral blood. In a pilot study, Nefussy et al (2010) examined the use cell subsets induced by G-CSF to slow down disease progression in patients with amyotrophic lateral sclerosis (ALS). Patients with definite or probable ALS were assigned in a double-blind manner to receive G-CSF or placebo every 3 months for 1 year. The primary outcome measure was the functional decline, measured by the revised ALS Functional Rating Scale, Revised (ALSFRS-R) score. Secondary outcome measures included vital capacity, manual muscle strength, compound muscle action potential amplitudes, neurophysiological index, and McGill single item quality of life score (QoL). A total of 39 patients were enrolled. Seventeen patients who received G-CSF and 18 who received placebo were evaluated. Granulocyte-CSF was effective in mobilizing CD34+ to blood. The outcome measures used showed no statistically significant benefit, although there was a trend of slowing disease progression following 2 G-CSF treatments, as shown by lower slopes of ALSFRS-R and QoL in the first 6 treatment months. The treatment had no major side-effects. The authors concluded that G-CSF administration in ALS patients caused successful mobilization of autologous bone marrow cells, but was not effective in slowing down disease deterioration.

In a Cochrane review, Minton et al (2010) evaluated the effectiveness of drugs for the management of cancer-related fatigue (CRF). These investigators searched the Cochrane Central Register of Controlled Trials (from Issue 2 2007) MEDLINE and EMBASE from January 2007 to October 2009 and a selection of cancer journals. They searched references of identified articles and contacted authors to obtain unreported data. Studies were included in the review if they meet the following criteria: (i) assessed drug therapy for
the management of CRF compared to placebo, usual care or a non-pharmacological intervention, (ii) RCTs, and (iii) adult patients with a clinical diagnosis of cancer. Two review authors independently assessed trial quality and extracted data. Meta-analyses were performed on different drug classes using continuous variable data. A total of 50 studies met the inclusion criteria; and 6 additional studies were identified since the original review. Only 31 of these studies involving 7,104 participants were judged to have used a sufficiently robust measure of fatigue and thus were deemed suitable for detailed analysis. The drugs were still analyzed by class (anti-depressants, hemopoietic growth factors, progestational steroids, as well as psychostimulants). Methylphenidate showed a small but significant improvement in fatigue over placebo (Z = 2.83; p = 0.005). Since the publication of the original review increased safety concerns have been raised regarding erythropoietin and this can not now be recommended in practice. The authors concluded that there is increasing evidence that psychostimulant trials provide evidence for improvement in CRF at a clinically meaningful level. There is still a requirement for a large scale RCT of methylphenidate to confirm the preliminary results. There is new safety data that indicates that the hemopoietic growth factors are associated with increased adverse outcomes. These drugs can no longer be recommended in the treatment of CRF.

In a multi-center RCT, Korzenik et al (2005) investigated the effectiveness of sargramostim in treating Crohn's disease. A total of 124 patients with moderate-to-severe active Crohn's disease were randomly assigned to receive 6 µg of sargramostim per kilogram of body weight per day or placebo subcutaneously for 56 days using a 2:1 ratio. The primary end point was a clinical response, defined by a decrease from baseline of at least 70 points in the Crohn's Disease Activity Index (CDAI) at the end of treatment (day 57). Other end points included changes in disease severity and the health-related quality of life and adverse events. There was no significant difference in the rate of the primary end point of a clinical response defined by a decrease of at least 70 points in the CDAI score on day 57 between the sargramostim and placebo groups (54 % versus 44 %, p = 0.28). However, significantly more patients in the sargramostim group than in the placebo group reached the secondary end points of a clinical response defined by a decrease from baseline of at least 100 points in the CDAI score on day 57 (48 % versus 26 %, p = 0.01) and of remission, defined by a CDAI score of 150 points or less on day 57 (40 % versus 19 %, p = 0.01). The rates of either type of clinical response and of remission were significantly higher in the sargramostim group than in the placebo group on day 29 of treatment and 30 days after treatment. The sargramostim group also had significant improvements in the quality of life. Mild-to-moderate injection-site reactions and bone pain were more common in the sargramostim group, and 3 patients in this group had serious adverse events possibly or probably related to treatment. These investigators concluded that although this study was negative for the primary end point, findings for the secondary end points suggested that sargramostim therapy decreased disease severity and improved the quality of life in patients with active Crohn's disease. The authors noted that the role of GM-CSF in the biology of Crohn's disease remains to be defined.

Tbo-filgrastim, a short-acting, synthetic form of G-CSF, is a biologic response modifier that binds to stem cells in bone marrow and stimulates the production of neutrophils. On August 29, 2012, the FDA approved the use of tbo-filgrastim (Neutroval) to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Tbo-filgrastim was evaluated in a clinical study of 348 adult patients with advanced breast cancer receiving treatment with the anti-cancer drugs doxorubicin and docetaxel. Patients were randomly assigned to receive tbo-filgrastim, a placebo, or a
non-U.S.-approved filgrastim product, a drug that also stimulates neutrophil production by the bone marrow. The effectiveness of tbo-filgrastim was determined based on study results that showed that patients receiving tbo-filgrastim recovered from severe neutropenia in 1.1 days compared with 3.8 days in those receiving the placebo.

In a Cochrane review, Moazzami and associates (2013) assessed the effects of stem cell mobilization following G-CSF therapy in patients with acute MI. These investigators searched CENTRAL (The Cochrane Library Issue 4, 2010), MEDLINE (1950 to week 3 of November 2010), EMBASE (1980 to week 48 of 2010), BIOSIS Previews (1969 to November 30, 2010), ISI Science Citation Index Expanded (1970 to December 4, 2010) and ISI Conference Proceedings Citation Index - Science (1990 to December 4, 2010). These researchers also checked reference lists of articles. They included RCTS involving participants with a clinical diagnosis of acute MI who were randomly allocated to the subcutaneous administration of G-CSF through a daily dose of 2.5, 5 or 10 microgram/kg for 4 to 6 days or placebo. No age or other restrictions were applied for the selection of patients. Two authors independently selected trials, assessed trials for eligibility and methodological quality, and extracted data regarding the clinical efficacy and adverse outcomes. Disagreements were resolved by the third author. These investigators included 7 trials reported in 30 references in the review (354 participants). In all trials, G-CSF was compared with placebo preparations. Dosage of G-CSF varied among studies, ranging from 2.5 to 10 microgram/kg/day. Regarding overall risk of bias, data regarding the generation of randomization sequence and incomplete outcome data were at a low-risk of bias; however, data regarding binding of personnel were not conclusive. The rate of mortality was not different between the 2 groups (RR 0.64, 95 % CI: 0.15 to 2.80, p = 0.55). Regarding safety, the limited amount of evidence is inadequate to reach any conclusions regarding the safety of G-CSF therapy. Moreover, the results did not show any beneficial effects of G-CSF in patients with acute MI regarding left ventricular function parameters, including left ventricular ejection fraction (RR 3.41, 95 % CI: -0.61 to 7.44, p = 0.1), end systolic volume (RR -1.35, 95 % CI: -4.68 to 1.99, p = 0.43) and end diastolic volume (RR -4.08, 95 % CI: -8.28 to 0.12, p = 0.06). It should also be noted that the study was limited since the trials included lacked long enough follow-up durations. The authors concluded that limited evidence from small trials suggested a lack of benefit of G-CSF therapy in patients with acute MI. Moreover, they stated that since data of the risk of bias regarding binding of personnel were not conclusive, larger RCTs with appropriate power calculations and longer follow-up durations are needed to address current uncertainties regarding the clinical effectiveness and therapy-related adverse events of G-CSF treatment.

In a Cochrane review, Bath and colleagues (2013) evaluated (i) the safety and effectiveness of CSFs in people with acute or subacute ischemic or hemorrhagic stroke, and (ii) the effect of CSFs on circulating stem and blood cell counts. These investigators searched the Cochrane Stroke Group Trials Register (last searched September 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 4), MEDLINE (1985 to September 2012), EMBASE (1985 to September 2012) and Science Citation Index (1985 to September 2012). In an attempt to identify further published, unpublished and ongoing trials, these researchers contacted manufacturers and principal investigators of trials (last contacted April 2012). They also searched reference lists of relevant articles and reviews. They included RCTs recruiting people with acute or subacute ischemic or hemorrhagic stroke. Colony-stimulating factors included stem cell factor (SCF), erythropoietin (EPO), G-CSF, GM-CSF, macrophage-colony stimulating factor (M-CSF, CSF-1), thrombopoietin (TPO), or analogs of these. The primary outcome
was functional outcome at the end of the trial. Secondary outcomes included safety at the end of treatment, death at the end of follow-up, infarct volume and hematology measures. Two review authors independently extracted data and assessed trial quality; they contacted study authors for additional information. These investigators included a total of 11 studies involving 1,275 participants. In 3 trials (n = 782), EPO therapy was associated with a significant increase in death by the end of the trial (odds ratio (OR) 1.98, 95% CI: 1.19 to 3.3, p = 0.009) and a non-significant increase in serious adverse events. Erythropoietin significantly increased the red cell count with no effect on platelet or white cell count, or infarct volume. Two small trials of carbamylated EPO have been completed but have yet to be reported. These researchers included 8 small trials (n = 548) of G-CSF. Granulocyte-CSF was associated with a non-significant reduction in early impairment (mean difference (MD) -0.4, 95% CI: -1.82 to 1.01, p = 0.58); but had no effect on functional outcome at the end of the trial. Granulocyte-CSF significantly elevated the white cell count and the CD34+ cell count, but had no effect on infarct volume. Further trials of G-CSF are ongoing. The authors concluded that there are significant safety concerns regarding EPO therapy for stroke. It is too early to know whether other CSFs improve functional outcome.

Poole and colleagues (2013) stated that many patients with peripheral artery disease (PAD) have walking impairment despite therapy. Experimental studies in animals demonstrated improved perfusion in ischemic hind limb after mobilization of bone marrow progenitor cells (PCs), but whether this is effective in patients with PAD is unknown. These researchers examined if therapy with GM-CSF improves exercise capacity in patients with intermittent claudication. In a phase II, double-blind, placebo-controlled study, 159 patients (median [SD] age, 64 [8] years; 87% male, 37% with diabetes) with intermittent claudication were enrolled at medical centers affiliated with Emory University in Atlanta, Georgia, between January 2010 and July 2012. Participants were randomized (1:1) to receive 4 weeks of subcutaneous injections of GM-CSF (leukine), 500 μg/day 3 times a week, or placebo. Both groups were encouraged to walk to claudication daily. The primary outcome was peak treadmill walking time (PWT) at 3 months. Secondary outcomes were PWT at 6 months and changes in circulating PC levels, ankle brachial index (ABI), and walking impairment questionnaire (WIQ) and 36-item Short-Form Health Survey (SF-36) scores. Of the 159 patients randomized, 80 were assigned to the GM-CSF group. The mean (SD) PWT at 3 months increased in the GM-CSF group from 296 (151) seconds to 405 (248) seconds (mean change, 109 seconds [95% CI: 67 to 151]) and in the placebo group from 308 (161) seconds to 376 (182) seconds (change of 56 seconds [95% CI: 14 to 98]), but this difference was not significant (mean difference in change in PWT, 53 seconds [95% CI: -6 to 112], p = 0.08). At 3 months, compared with placebo, GM-CSF improved the physical functioning subscore of the SF-36 questionnaire by 11.4 (95% CI: 6.7 to 16.1) versus 4.8 (95% CI: -0.1 to 9.6), with a mean difference in change for GM-CSF versus placebo of 7.5 (95% CI: 1.0 to 14.0; p = 0.03). Similarly, the distance score of the WIQ improved by 12.5 (95% CI: 6.4 to 18.7) versus 4.8 (95% CI: -0.2 to 9.8) with GM-CSF compared with placebo (mean difference in change, 7.9 [95% CI: 0.2 to 15.7], p = 0.047). There were no significant differences in the ABI, WIQ distance and speed scores, claudication onset time, or mental or physical component scores of the SF-36 between the groups. The authors concluded that therapy with GM-CSF 3 times a week did not improve treadmill walking performance at the 3-month follow-up. The improvements in some secondary outcomes with GM-CSF suggested that it may warrant further study in patients with claudication. In addition, further investigation is needed to investigate the variability of responsiveness to GM-CSF and its clinical significance.
Siristatidis et al (2013) noted that GM-CSF is a cytokine/growth factor produced by epithelial cells that exerts embryotrophic effects during the early stages of embryo development. These investigators performed a systematic review, and 6 studies that were performed in humans undergoing assisted reproduction technologies (ART) were located. They examined if embryo culture media supplementation with GM-CSF could improve success rates. As the type of studies and the outcome parameters investigated were heterogeneous, these researchers decided not to perform a meta-analysis. Most of the studies had a trend favoring the supplementation with GM-CSF, when outcomes were measured in terms of increased percentage of good-quality embryos reaching the blastocyst stage, improved hatching initiation and number of cells in the blastocyst, and reduction of cell death. However, no statistically significant differences were found in implantation and pregnancy rates in all apart from 1 large multi-center trial, which reported favorable outcomes, in terms of implantation and live birth rates. The authors proposed properly conducted and adequately powered RCTs to further validate and extrapolate the current findings with the live birth rate to be the primary outcome measure.

In a Cochrane review, Cruciani et al (2013) examined the effects of adjunctive G-CSF compared with placebo or no growth factor added to usual care on rates of infection, cure and wound healing in people with diabetes who have a foot infection. These investigators searched the Cochrane Wounds Group Specialised Register (searched March 14, 2013); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 2); Ovid MEDLINE (1948 to week 1 of March 2013); Ovid EMBASE (1974 to March 13, 2013); Ovid MEDLINE (In-Process March 13,2013); and EBSCO CINAHL (1982 to February 28, 2013). Randomized controlled trials that evaluated the effect of adding G-CSF to usual care in people with a diabetic foot infection were included for analysis. Three review authors independently assessed trial eligibility, methodological quality and extracted data. They reported RR or, for continuous outcomes, MD, with 95 % CI. In the case of low or no heterogeneity these researchers pooled studies using a fixed-effect model. They identified and included 5 eligible trials with a total of 167 patients. The investigators administered various G-CSF preparations, at different doses and for different durations of time. Adding G-CSF did not significantly affect the likelihood of resolution of infection or wound healing, but it was associated with a significantly reduced likelihood of lower extremity surgical interventions (RR 0.38; 95 % CI: 0.21 to 0.70), including amputation (RR 0.41; 95 % CI: 0.18 to 0.95). Moreover, providing G-CSF reduced the duration of hospital stay (MD -1.40 days; 95 % CI: -2.27 to -0.53 days), but did not significantly affect the duration of systemic antibiotic therapy (MD -0.27 days; 95 % CI: -1.30 to 0.77 days). The authors concluded that the available evidence is limited, but suggests that adjunctive G-CSF treatment in people with a diabetic foot infection, including infected ulcers, does not appear to increase the likelihood of resolution of infection or healing of the foot ulcer. However, it does appear to reduce the need for surgical interventions, especially amputations, and the duration of hospitalization. Clinicians might consider adding G-CSF to the usual treatment of diabetic foot infections, especially in patients with a limb-threatening infection, but it is not clear which patients might benefit.

In a phase I/II clinical trial, Saberi et al (2014) examined the effect of spinal cord injury (SCI) severity on the neurological outcomes, after neuroprotective treatment for SCI with G-CSF. A total of 74 consecutive patients with SCI of at least 6 months duration, with stable neurological status in the last 3 months having informed consent, for the treatment were included in the study. All the patients had undergone at least 3 months of standard rehabilitation. Patients were assessed by American Spinal Injury Association (ASIA) scale,
Hematopoietic Colony-Stimulating Factors (CSFs)

Spinal Cord Independence Measure (SCIM) III, and International Association of Neurorestitution—Spinal Cord Injury Functional Rating Scale (IANR-SCIFRS) just before intervention and periodically until 6 months after subcutaneous administration of 5 g/kg per day of G-CSF for 7 consecutive days. Multiple linear regression models, was performed for statistical evaluation of lesion completeness and level of injury on changes in ASIA motor, light touch, pinprick, IANR-SCIFRS, and SCIM III scores, as a phase I/II, comparative study. The study consisted of 52 motor complete, and 22 motor incomplete SCI patients. There was not any significant difference regarding age and sex, chronicity, and level of SCI between the 2 groups. Motor incomplete patients had significantly more improvement in ASIA motor score compared to the motor complete patients (7.68 scores, \( p < 0.001 \)) also they had significant improvement in light touch (6.42 scores, \( p = 0.003 \)) and pin-prick sensory scores (4.89 scores, \( p = 0.011 \)). Therefore, G-CSF administration in motor incomplete SCIs is associated with significantly higher motor improvement, and also the higher the initial ASIA Impairment Scale (AIS) grade, the less would be the final AIS change, and incomplete cases are more welcome into the future studies. The clinical value of G-CSF in patients with chronic spinal cord injuries need to be further investigated in phase III clinical studies.

Chung et al (2014) investigated the effects of G-CSF on glial scar formation after SCI in rats and compared the therapeutic effects between G-CSF and GM-CSF to evaluate G-CSF as a potential substitute for GM-CSF in clinical application. Rats were randomly assigned to 1 of 4 groups: (i) a sham-operated group (Group 1), (ii) an SCI group without treatment (Group 2), (iii) an SCI group treated with G-CSF (Group 3), and (iv) an SCI group treated with GM-CSF (Group 4). Granulocyte-colony stimulating factor and GM-CSF were administered via intra-peritoneal injection immediately after SCI. The effects of G-CSF and GM-CSF on functional recovery, glial scar formation, and axonal regeneration were evaluated and compared. The rats in Groups 3 and 4 showed better functional recovery and more decreased cavity sizes than those in Group 2 (\( p < 0.05 \)). Both G-CSF and GM-CSF suppressed intensive expression of glial fibrillary acidic protein around the cavity at 4 weeks and reduced the expression of chondroitin sulfate proteoglycans (\( p < 0.05 \)). Also, early administration of G-CSF and GM-CSF protected axon fibers from destructive injury and facilitated axonal regeneration. There were no significant differences in comparisons of functional recovery, glial scar formation, and axonal regeneration between G-CSF and GM-CSF. The authors concluded that G-CSF suppressed glial scar formation after SCI in rats, possibly by restricting the expression of glial fibrillary acidic protein and chondroitin sulfate proteoglycans, which might facilitate functional recovery from SCI. They stated that GM-CSF and G-CSF had similar effects on glial scar formation and functional recovery after SCI, suggesting that G-CSF can potentially be substituted for GM-CSF in the treatment of SCI. The findings from this animal study need to be validated in well-designed human trials.

Appendix

Table: Selected Chemotherapy Regimens with Incidence of Febrile Neutropenia of 20 % or higher

<table>
<thead>
<tr>
<th>Cancer Histology</th>
<th>Stage and Prior Therapy</th>
<th>Regimen</th>
<th>Febrile Neutropenia (%)</th>
</tr>
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</table>

http://qawww.aetna.com/cpb/medical/data/1_99/0055_draft.html

03/25/2015
Hematopoietic Colony-Stimulating Factors (CSFs)

Adapted from Smith et al, 2006.

Key: CBDCA/Pac = carboplatin, paclitaxel; TAC = docetaxel, doxorubicin, cyclophosphamide; AT = doxorubicin, docetaxel; TAC = docetaxel, doxorubicin, cyclophosphamide; Doc = docetaxel; VelP = vinblastine, ifosfamide, cisplatin; Topo = topotecan; CAV = cyclophosphamide, doxorubicin, vincristine; VAPEC-B = vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin; ESHAP = etoposide, methylprednisolone, Ara-C, cisplatin; DHAP = dexamethasone, cisplatin, cytarabine

Table: FDA-Approved Labeling of Hematopoietic Colony-Stimulating Factors

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<tr>
<th>Drug</th>
<th>Indication</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen</td>
<td>Myelosuppressive chemotherapy (adults)</td>
<td>5 mcg/kg/day. Dosage increased in increments of 5 mcg/kg/day for each chemotherapy cycle, according to duration and severity of ANC nadir</td>
</tr>
<tr>
<td>Bone marrow transplant for cancer (adults)</td>
<td>10 mcg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood progenitor cell mobilization</td>
<td>10 mcg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Indications</td>
<td>Dosage</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Leukine (sargramostim)</td>
<td>All FDA-approved indications</td>
<td>250 mcg/m2/day</td>
</tr>
<tr>
<td>Neulasta (pegfilgrastim)</td>
<td>All FDA-approved indications</td>
<td>6 mg per chemotherapy cycle</td>
</tr>
<tr>
<td>Neutroval (tbo-filgrastim)</td>
<td>Myelosuppressive chemotherapy (adults)</td>
<td>5 mcg/kg/day. Dosing should continue until the expected nadir has passed and the neutrophil count has recovered to the normal range.</td>
</tr>
</tbody>
</table>

Key: ANC = absolute neutrophil count; mcg = micrograms; kg = kilograms; m2 = square meters.

Source: FDA-approved labeling.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

36511 - 36516  Therapeutic apheresis
38240 - 38242  Bone marrow or blood-derived peripheral stem cell transplantation
96372  Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96401 - 96549  Chemotherapy administration
99601 - 99602  Home infusion procedures/services

HCPCS codes covered if selection criteria are met:

J1442  Injection, filgrastim (g-csf), 1 microgram
J1446  Injection, tbo-filgrastim, 5 micrograms
J2505  Injection, pegfilgrastim, 6 mg
J2820  Injection, sargramostim (GM-CSF), 50 mcg

Other HCPCS codes related to the CPB:

J1570  Injection, gancyclovir sodium, 500 mg
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3485</td>
<td>Injection, zidovudine, 10 mg</td>
</tr>
<tr>
<td>J7310</td>
<td>Ganciclovir, 4.5 mg, long-acting implant</td>
</tr>
<tr>
<td>J7506</td>
<td>Prednisone, oral, per 5 mg</td>
</tr>
<tr>
<td>J8510</td>
<td>Bulsulfan; oral 2 mg</td>
</tr>
<tr>
<td>J8530</td>
<td>Cyclophosphamide; oral, 25 mg</td>
</tr>
<tr>
<td>J8560</td>
<td>Etoposide; oral, 50 mg</td>
</tr>
<tr>
<td>J8600</td>
<td>Melphalan; oral 2 mg</td>
</tr>
<tr>
<td>J8610</td>
<td>Methotrexate; oral, 2.5 mg</td>
</tr>
<tr>
<td>J9000</td>
<td>Injection, doxorubicin HCl, 10 mg</td>
</tr>
<tr>
<td>J9001</td>
<td>Injection, doxorubicin HCl, all lipid formulations, 10 mg</td>
</tr>
<tr>
<td>J9045</td>
<td>Injection, carboplatin, 50 mg</td>
</tr>
<tr>
<td>J9050</td>
<td>Injection, carmustine, 100 mg</td>
</tr>
<tr>
<td>J9065</td>
<td>Injection, cladribine, per 1 mg</td>
</tr>
<tr>
<td>J9070</td>
<td>Cyclophosphamide, 100 mg</td>
</tr>
<tr>
<td>J9098</td>
<td>Injection, cytarabine liposome, 10 mg</td>
</tr>
<tr>
<td>J9100</td>
<td>Injection, cytarabine, 100 mg</td>
</tr>
<tr>
<td>J9120</td>
<td>Injection, dactinomycin, 0.5 mg</td>
</tr>
<tr>
<td>J9130</td>
<td>Dacarbazine, 100 mg</td>
</tr>
<tr>
<td>J9150</td>
<td>Injection, daunorubicin, 10 mg</td>
</tr>
<tr>
<td>J9151</td>
<td>Injection, daunorubicin citrate, liposomal formulation, 10 mg</td>
</tr>
<tr>
<td>J9171</td>
<td>Injection, Docetaxel, 1 mg [Taxotere]</td>
</tr>
<tr>
<td>J9181</td>
<td>Injection, etoposide, 10 mg</td>
</tr>
<tr>
<td>J9185</td>
<td>Injection, fludarabine phosphate, 50 mg</td>
</tr>
<tr>
<td>J9190</td>
<td>Injection, fluorouracil, 500 mg</td>
</tr>
<tr>
<td>J9200</td>
<td>Injection, flouxuridine, 500 mg</td>
</tr>
<tr>
<td>J9208</td>
<td>Injection, ifosfamide, 1 g</td>
</tr>
<tr>
<td>J9230</td>
<td>Injection, mechlorethamine HCl, (nitrogen mustard), 10 mg</td>
</tr>
<tr>
<td>J9245</td>
<td>Injection, melphalan HCl, 50 mg</td>
</tr>
<tr>
<td>J9250</td>
<td>Methotrexate sodium, 5 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>J9260</td>
<td>Methotrexate sodium, 50 mg</td>
</tr>
<tr>
<td>J9265</td>
<td>Injection, paclitaxel, 30 mg</td>
</tr>
<tr>
<td>J9267</td>
<td>Injection, paclitaxel, 1 mg</td>
</tr>
<tr>
<td>J9270</td>
<td>Injection, plicamycin, 2.5 mg</td>
</tr>
<tr>
<td>J9280</td>
<td>Injection, mitomycin, 5 mg</td>
</tr>
<tr>
<td>J9293</td>
<td>Injection, mitoxantrone HCl, per 5 mg</td>
</tr>
<tr>
<td>J9340</td>
<td>Injection, thiotepa, 15 mg</td>
</tr>
<tr>
<td>J9360</td>
<td>Injection, vinblastine sulfate, 1 mg</td>
</tr>
<tr>
<td>J9370</td>
<td>Vincristine sulfate, 1 mg</td>
</tr>
<tr>
<td>J9390</td>
<td>Injection, vinorelbine tartrate, 10 mg</td>
</tr>
<tr>
<td>Q0083 - Q0085</td>
<td>Chemotherapy administration</td>
</tr>
<tr>
<td>Q2017</td>
<td>Injection, teniposide, 50 mg</td>
</tr>
<tr>
<td>Q2050</td>
<td>Injection, doxorubicin hydrochloride, liposomal, not otherwise specified, 10 mg</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications including pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days pre- and post-transplant care in the global definition</td>
</tr>
<tr>
<td>S9537</td>
<td>Home therapy; hematopoietic hormone injection therapy (e.g. erythropoietin, G-CSF, GM-CSF); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

**ICD-9 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>042</td>
<td>Human immunodeficiency virus [HIV] disease</td>
</tr>
<tr>
<td>140.0 - 184.9, 186 - 209.36, 209.75</td>
<td>Malignant neoplasms [except routine use as prophylaxis, for chemosensitization of myeloid leukemias, for post-allogeneic transplant support in myeloid malignancies, to increase dose-intensity or schedule of cytotoxic chemo beyond established ranges, in members receiving concomitant radiation, or for &quot;priming&quot; effects]</td>
</tr>
<tr>
<td>238.72 - 238.75</td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>260 - 269.9</td>
<td>Nutritional deficiencies</td>
</tr>
</tbody>
</table>
Neutropenia, unspecified [febrile]
Congenital neutropenia
Cyclic neutropenia
Drug induced neutropenia [except interferon-induced]
Neutropenia due to infection
Other neutropenia
Late effect of radiation
Complication of bone marrow transplant
Organ or tissue replaced by transplant, bone
Bone marrow replaced by transplant [except post allogeneic transplant support in myeloid malignancies]
Peripheral stem cells replaced by transplant [except post allogeneic transplant support in myeloid malignancies]
Donors, blood, stem cells
Donors, bone marrow
Convalescence and palliative care following chemotherapy

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

Acute hepatitis C with hepatic coma
Chronic hepatitis C with hepatic coma
Acute hepatitis C without mention of hepatic coma
Chronic hepatitis C without mention of hepatic coma
Unspecified viral hepatitis C
Malignant melanoma of skin
Malignant neoplasm of prostate
Carcinoma in situ of prostate
Aplastic anemia
Amyotrophic lateral sclerosis
Acute myocardial infarction
Occlusion and stenosis of precerebral arteries, occlusion of cerebral arteries, transient cerebral ischemia, and acute, but ill-defined, cerebrovascular disease [stroke]
440.20 - 440.22  Atherosclerosis of the arteries of the extremities
443.0 - 443.9  Other peripheral vascular disease
480.0 - 487.0  Pneumonia [other than febrile, neutropenic persons]
555.0 - 555.9  Regional enteritis
621.5  Intrauterine synechiae [Ashermanâ€™s syndrome]
628.0 - 628.9  Infertility, female
714.1  Felty's syndrome
771.81  Septicemia [sepsis] of newborn [preterm neonates]
780.79  Other malaise and fatigue [cancer-related]
V42.0  Kidney replaced by transplant

Other ICD-9 codes related to the CPB:

001.0 - 139.8  Infectious and parasitic diseases
279.00 - 279.9  Disorders involving the immune mechanism
458.0 - 458.9  Hypotension
461.0 - 461.9  Acute sinusitis
473.0 - 473.9  Chronic sinusitis
528.00 - 528.9  Diseases of the oral soft tissues, excluding lesions specific for gingiva and tongue
682.0 - 682.9  Other cellulitis and abscess
771.81 - 771.89  Other infections specific to the perinatal period [not covered for prophylactic reduction of sepsis and improvement of survival in pre-term neonates]
780.60 - 780.61  Fever
870.0 - 897.7  Open wound
990  Effects of radiation, unspecified
995.90 - 995.94  Systemic inflammatory response syndrome (SIRS)
E933.1  Adverse effect of antineoplastic and immunosuppressive drugs
V58.0  Encounter for radiotherapy
V58.11 - V58.12  Encounter for antineoplastic chemotherapy and immunotherapy
V58.62  Long-term (current) use of antibiotics
The above policy is based on the following references:


83. del Giglio A, Eniu A, Ganea-Motan D, et al. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer. 2008;8:332.


91. All Wales Medicines Strategy Group (AWMSG). Filgrastim (TevaGrastim®), AWMSG Secretariat Assessment Report Advice No. 1410. Penarth, UK: All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG); 2010.


