Colony-stimulating factors: clinical evidence for treatment and prophylaxis of chemotherapy-induced febrile neutropenia

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The hematopoietic growth factors (HGFs) are a family of glycoproteins which plays a major role in the proliferation, differentiation, and survival of primitive hematopoietic stem and progenitor cells, and in the functions of some mature cells. More than 20 different molecules of HGF have been identified. Among them, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been demostrated to be effective in reducing the incidence of febrile neutropenia when administered inmediately after chemotherapy and as supportive therapy in patients undergoing bone marrow transplantation. Chemotherapy used for treatment of cancer often causes neutropenia, which may be profound, requiring hospitalization, and leading to potentially fatal infection. The uses of the recombinant human hematopoietic colony-stimulating factors G-CSF and GM-CSF for treatment and prophylaxis of chemotherapy-induced febrile neutropenia will be reviewed here.

Key words: hematopoietic growth factors, colony-stimulating factors, febrile neutropenia, chemotherapy induced neutropenia, dose intensity, chemotherapy.

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INTRODUCTION

HGF are cytokines secreted by a wide variety of cell types and act broadly upon target hematopoietic cells through receptor mediated signals[1,4]. G-CSF regulates the production of neutrophil lineage. The administration of G-CSF to human results in a dose-dependent increase in circulating neutrophils mainly because of a reduced transit time from stem cell to mature neutrophil. GM-CSF stimulates the growth of granulocyte, macrophage, and eosinophil colonies. Administration of GM-CSF to human results in a dose-dependent increase in blood neutrophils, eosinophils, macrophages, and sometimes lymphocytes. That cytokines are also known to enhance neutrophil function. Different types of G-CSF and GM-CSF have been tested in clinical trials. Among the most used GM-CSF are sargramostim, molgastrim and regramostrim, and among the most used G-CSF are filgastrim and lemogastrim. A next-generation G-CSF, pegfilgastrim, was bioengineered for sustained duration of action by the addition of a 20 kD polyethilene glycol (PEG) moiety to the N-terminus of the G-CSF molecule, increasing molecular size and diminishing renal filtration, and resulted in prolonged circulation in the serum with eventual elimination by binding to G-CSF receptors on recovering neutrophils.

The efficacy of recombinant human G-CSF or GM-CSF for the prevention of FN in patients with chemotherapy-induced neutropenia varies with the clinical setting (ie, primary prophylaxis versus the treatment of patients who already have FN), the presence of underlying damage to the patient's hematopoietic stem cells, the intensity of chemotherapy (ie, myeloablative versus non-myeloablative), the concurrent use of radiation, and the overall clinical status of the patient (ie, age and comorbid conditions). Both G-CSF and GM-CSF have been demostrated to be effective in reducing the incidence of FN when administered inmediately after chemotherapy[2,3], but results of randomized clinical studies designed to asses their role as adjunt therapy to antibiotics in FN were not clear and conflicting results appeared[5-15]. In 2000, the American Society of Clinical Oncology (ASCO) updated guidelines for the administration of HGF for the treatment of chemotherapy-induced neutropenia[11] and, on the basis of the results of these randomized trials, the routine use of CSF in the treatment of FN was not recommended. In this article, we have carried out a review about clinical evidence use of HGF

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for treatment and prophylaxis of chemotherapy-induced FN.

CLINICAL USES OF CSF IN PATIENTS RECEIVING CANCER CHEMOTHERAPY

CSF have been given as either prophylaxis or therapy to patients on myeloablative (dose-intensive) chemotherapy that usually leads to prolonged neutropenia. Mosts of its use has been in patients with acute myelogenous leukemia (AML), Hodgkin's and non-Hodgkin's lymphoma, sarcomas, seminomas and small cell carcinomas of the lung. GM-CSF is commonly used to ameliorate the neutropenia seen during dose-intensive chemotherapy as well as to support patients who are neutropenic as a result of myelodysplastic syndrome (MDS) or aplastic anemia.

A) Primary administration

The 2000 update American Society of Clinical Oncology evidence-clinical practice guidelines for the use of CSFs includes several important recommendations[11]. Routine administration of myeloid growth factors for prophylaxis in previously untreated patients is not recommended for most chemotherapeutic regimens. Guidelines from the Infectious Diseases Society of America (IDSA) also support this position[12]. Exceptions might include[16]:

- Patients who are at higher risk for FN or infection because of preexisting neutropenia due to the baseline disease or extensive prior chemotherapy or radiation therapy.
- When coexisting conditions are present that could potentially enhance the risk for serious infection, such as altered immune function, open wounds, ongoing infection, poor performance status, and more advanced cancer.

The most compelling evidence of benefit has come from controlled trials in which the incidence of FN was at least 40% in the control group; in this setting, the administration of CSF produces an approximately 50% reduction in the incidence of FN in adults[6-15]. These benefits were confirmed in a meta-analysis that included 1144 patients treated on eight randomized controlled trials[17]. Prophylactic G-CSF was associated with a 62% reduction in the risk of FN (OR 0.38. $p < 0.0001$), and a significant reduction in documented infection (OR 0.51, $p < 0.001$), while there was only a nonsignificant trend towards reduced infection-related mortality. The reduction in treatment-related neutropenia made possible by prophylactic G-CSF may permit dose intensity to be maintained in patients treated with curative intent (eg, lymphoma, adjuvant treatment for breast cancer). The use of G-CSF illustrated in a controlled trial in which 80 patients with high-grade non-Hodgkin's lymphoma was associated with less grade 4 neutropenia (37 versus 85%) and FN (22 versus 44%), and as a result, these patients were significantly less likely to require chemotherapy dose reduction (10 versus 33%)[18].

In a more recent review, the National Comprehensive Cancer Network (NCCN) has published guidelines for HGF, which recommend routine prophylactic use of CSF in patients receiving systematic chemotherapy at high risk (>20%) of developing FN or related complications that may compromise treatment[19], while 2000 ASCO guidelines recommends CSF in patients who have a > 40% chance of developing neutropenia after high-dose intensive chemotherapy[11]. It is mainly due to a recent cost-minimization analysis of pegfilgrastim based on risk and efficacy estimated from an updated meta-analysis[20] and recent multi-institutional hospital and physician cost data have been presented[21]. Risk thresholds for FN under 20% were estimated with increasing cost savings as the risk reduction associated with primary prophylaxis with pegfilgastrim increases. It should be noted that these economic models are based on cycle-events, with the assumption that similar risks will be experienced across cycles of the same regimen when administered without reductions in dose intensity or the addition of a myeloid growth factor.

In comparison to apparent efficacy in high-risk patients, the routine use of G-CSF prophylaxis in patients treated with standard-dose chemotherapy in which the incidence of FN is less than 20% is expensive and not associated with an obvious therapeutic benefit or cost savings[22].

There also appears to be little value of G-CSF therapy in patients with severe afebrile neutropenia. In a controlled trial with 138 afebrile outpatients with severe chemotherapy-induced neutropenia (ANC 500/µl), the duration of severe neutropenia was modestly shorter with G-CSF (2 versus 4 days), but there was no effect on the rate of hospitalization or number of culture-positive infections[25].

Acute myeloid leukemia

Several randomized studies have been conducted to evaluate the use of CSFs begun after induction therapy in patients with AML, especially elderly patients[24-30]. In almost all of these studies, the addition of CSFs decreased the time to recovery to 500 neutrophils/mm^3 by two to six days. The nadir is not affected and effects on the incidence of severe infection, antibiotic usage, and the duration of hospitalization have been variable. It has been suggested that there may be greater benefit from HGF in elderly patients who are particularly susceptible to infection and experience a higher infectious mortality rate during episodes of neutropenia. However, although the duration of neu-

tropenia has been reduced by the use of CSFs, these trials have largely been disappointing searching for beneficial effect in treatment-related morbidity or mortality[5,24,27].

However, caution should be exercised in patients with AML because of concerns that GM-CSF may stimulate the leukemic clonal cells[31,32]. CSF administration generally should be reserved for cycles after induction chemotherapy.

Concomitant chemotherapy and radiation

Patients receiving concomitant chemotherapy and radiation, particularly involving the mediastinum, show higher incidence of thrombocytopenia. In one study which included 215 patients with small cell lung cancer who have received concurrent chemotherapy and thoracic radiotherapy with or without GM-CSF, the incidence of grade 3 and 4 thrombocytopenia was significantly higher in the GM-CSF arm (91 versus 18%)[33]. In spite of the benefit of CSF for reversal of radiation-induced neutropenia, deleterious effects on platelet counts have deterred their clinical use in the setting of combined modality therapy.

B) Secondary prophylaxis

Secondary prophylaxis refers to the administration of a CSF in later cycles after FN has occurred in a prior cycle. The goal is to maintain chemotherapy dose intensity when dose reduction is not desired. No published regimen has shown improved disease-free or overall survival when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. Excluding those tumors that are curable (eg, germ cell tumors), dose reduction after an episode of severe FN should be considered as the primary treatment rather than the use of CSFs[11].

C) Adjunctive treatment for febrile neutropenic patients

The benefit of CSF therapy as adjuvant treatment to antibiotics for FN has not been definitively proven in patients with uncomplicated fever and neutropenia (defined as fever of 10 days in duration, no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection, and no uncontrolled malignancies). As a result, the available current data also do not support the routine use of CSFs as an adjunct to antimicrobial therapy in patients with FN[11]. Certain patients with fever and neutropenia may be at higher risk for infection-associated complications, and have prognostic factors that are predictive of poor outcome (eg, ANC < 100/µl, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction or invasive fungal infection). CSFs may be indicated in such situations, although a beneficial effect in these circumstances has not been definitively proven[11].

In a recent meta-analysis that included 1518 patients treated on 13 randomized controlled trials, the overall mortality was not influenced significantly by the use of CSF (OR 0.68, p = 0.1), but a significant result was obtained for the use of CSF in reducing infection-related mortality (OR 0.51, p = 0.05), and patients treated with CSFs had a shorter length of hospitalization (*hazard ratio* 0.63, p = 0.0006) and a shorter time to neutrophil recovery (*hazard ratio* 0.32, p < 0.00001)[34]. In subgroup analysis, patients with hematologic malignancies may benefit in terms of reduced mortalitiy for the use of CSF, although the results are highly influenced by Aviles et al[35] trial that showed a stronger effect of CSF, and if this study is excluded from analysis, the effect is no longer significant. In meta-analysis, authors recommend caution in interpretation of these results, but a possible effect on infection-related mortality may occur in patients with ANC < 100/µl related to chemotherapy in patients with hematologic malignancies.

DRUG DOSAGE AND SCHEDULES

In adults, the recommended dose of G-CSF is 5 µg/kg per day and 250 µg/m^2 per day for GM-CSF for all clinical situations other than peripheral blood progenitor cell mobilization, in which case a dose of 10 µg/kg per day has been recommended[11]. The preferred route is by subcutaneous injection.

Therapy is usually begun 24 to 72 hours after cessation of chemotherapy and is often continued until the absolute neutrophil count reaches 10,000/µl. However, a shorter duration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost. G-CSF should not be given in the period 24 hours before treatment with the next cycle of chemotherapy. CSF should probably not be given concurrently with chemotherapy (ie, not in the same day), and they should be discontinued several days before the next chemotherapy doses.

CLINICAL TOXICIY OF CSF

GM-CSF and G-CSF have been tested in multiple clinical trials and have in general been well tolerated. Both GM-CSF and G-CSF have been associated with bone pain, coincident with or shortly after administration. Occasional increases in leukocyte alkaline phosphatase and/or serum lactate dehydrogenase also have been noted. The major toxicities associated with CSF include flu-like symptoms, as fever, flushing, malaise, myalgia, arthralgia, anorexia, headache, and mild elevations of serum aminotransferases and

rash. These effects are usually mild, are alleviated by antipyretics, and disappear with continued administration. More serious GM-CSF toxicity has been observed at higher dose levels (> 32 µg/kg per day intravenously or > 15 µg/kg per day subcutaneously), as a capillary leak syndrome manifested by weight gain due to fluid retention, pericardial or pleural effusions, ascites, and/or edema[8,36], or a transient respiratory distress syndrome (possibly secondary to pulmonary sequestration of neutrophils or to capillary leak). The more glycosylated yeast derived form of GM-CSF (sargramostin) appears to be less likely to cause these dose-related toxicities than the bacterially derived products. Pathogenic neutrophil infiltration (acute febrile neutrophilic dermatosis or Sweet's syndrome) and cutaneous necrotizing vasculitis (leukocytoclastic vasculitis) can occur in selected patients with G-CSF[36,39,40].

POSSIBLE STIMULATION OF MALIGNANCY

Because HGF receptors are expressed by hematopoietic and several nonhematopoietic cell types, there has been a concern that certain malignant cell lineages might respond to such therapy, potentially worsening the underlying condition. There is a theoretical concern that G-CSF might induce or accelerate the development of AML or MDS with monosomy seven in aplastic anemia and infantile agranulocytosis (Kostmann disease)[4,41]. However, at present there is no evidence to support this hypotesis and have not shown any impact on the acceleration or development of AML in patients with either AML or MDS, but it is possible that long-term administration of G-CSF interacts with immunosuppressive therapy in patients with aplastic anemia[42,44].

ANTIBODIES TO RECOMBINANT GROWTH FACTORS

Recombinant human GM-CSF that is produced in mammalian cells (Chinese hamster ovary cells) is variably glycosylated on both O-linked and N-linked sites, while production in *E. coli* results in nonglycosylated GM-CSF, or the yeast product is glycosylated only at N-linked sites. All three products appear to be equally effective, but antibodies have been reported more frequently in patients given the yeast-derived product in phase I/II studies[45]. The IgG antibodies developed within seven days after the start of the infusion in all patients. Antibodies were non-neutralizing as judged by bone marrow colony-forming assay, and were directed at sites on the protein backbone of the GM-CSF molecule that are normally protected by O-linked glycosylation, but which are exposed in the yeast and *E. coli*-derived products.

POSSIBLE ENHANCEMENT OF HIV REPLICATION

A concern with GM-CSF therapy, but not G-CSF, in patients with AIDS is the potential for stimulation of HIV replication. This phenomenon was initially demonstrated *in vitro* experiments with mononuclear phagocytes exposed to GM-CSF[46]. Later *in vitro* studies revealed upregulation of CCR5 coreceptor expression and enhanced HIV infectivity in fresh human monocytes exposed to GM-CSF[47]. However, *in vivo* data on the relationship between GM-CSF therapy and HIV replication have been conflicting.

CONCLUSSIONS

GM-CSF and G-CSF enhances the production and half life of neutrophils and monocyte/macrophages and increases the microbicidal activity of these cells. Subcutaneous administration of CSF shortens the period of neutropenia in patients undergoing dose-intensive chemotherapy with no influence on the incidence of infections or mortality.

Side effects of CSF use, as bone pain, joint pain, and flu-like syndromes are comon and, in some reports, intense but are not life threatening. With higher doses of CSF, adverse effects become more frequent and more severe.

RECOMMENDATIONS

Primary prophylaxis

- Routine use of CSFs for primary prophylaxis before FN is indicated by the existing data in the following situations[11,16]:
  - Patients who are at higher risk for FN or infection because of preexisting neutropenia due to the baseline disease or extensive prior chemotherapy or radiation therapy.
  - When coexisting conditions are present that could potentially enhance the risk for serious infection, such as altered immune function, open wounds, ongoing infection, poor performance status, and more advanced cancer.
  - Patients who have a > 20% chance of developing neutropenia after high-dose intensive chemotherapy[20].
- CSF are not recommended as prophylaxis in an attempt to increase dose-intensity unless the expected incidence of FN is 40% or more, and the regimen is applied in a curative intent fashion[11].
- Primary administration of a CSF in AML is recommended after completion of induction chemotherapy to shorten the duration of neutropenia if benefits in terms of shortening the duration of hospitalization outweigh the costs of CSF use[11].

- Use of CSF should be avoided in patients receiving concomitant chemotherapy and radiation due to higher incidence of thrombocytopenia. For patients receiving radiation therapy involving large fields but no chemotherapy, therapeutic use of CSF may be considered if prolonged delays secondary to neutropenia are expected[11].

Secondary prophylaxis

- Except in the setting of curable tumors (eg, germ cell cancer), dose reduction after an episode of severe neutropenia should be considered the primary therapeutic option.

Adjuntive treatment for FN

- CSF therapy as adjuvant treatment to antibiotics for afebrile or febrile neutropenia are not recommended in patients with uncomplicated fever and neutropenia (defined as fever of 10 days in duration, no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection, and no uncontrolled malignancies).
- CSFs may be indicated in patients with pneumonia, sepsis syndrome or fungal infection, conditions known to have high morbidity and mortality, although a beneficial effect in these circumstances has not been definitively proven.

References

1. Holter JL, Ozer H. Hematopoietic Therapy: Hematopoietic Growth Factors. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: Principles and Practice of Oncology (ed 7). Philadelphia, PA: Lippincott Williams & Wilkins, 2001. p. 2442-59.
2. Freyer G, Ligneau B, Trillet-Lenoir V. Colony-stimulating factors in the prevention of solid tumors induced by chemotherapy in patients with febrile neutropenia. Int J Antimicrob Agents. 1998;10:5-9.
3. Lyman GH, Kuderer NM, Djulbegovic B. A meta-analysis of granulocyte colony-stimulating factor (rH-G-CSF) to prevent febrile neutropenia (FN) in patients receiving cancer chemotherapy. Am J Med. 2002;112:406-11.
4. Root RK, Dale DC. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in nonneutropenic patients. J Infect Dis. 1999;179 Suppl 2: S342-52.
5. Anaissie EJ, Vartivarian S, Bodey GP, et al. Randomized comparison between antibiotics alone and antibiotics plus granulocyte-macrophage colony-stimulating factor (*Escherichia coli*-derived) in cancer patients with fever and neutropenia. Am J Med. 1996;100:17-23.
6. Maher DW, Lieschke GJ, Green M, et al. Filgrastim in patients with chemotherapyinduced febrile neutropenia: A double-blind, placebo-controlled trial. Ann Intern Med. 1994;121:492-501.
7. Riikonen P, Saarinen UM, Makipernaa A, et al. Recombinant human granulocyte-macrophage colony-stimulating factor in the treatment of febrile neutropenia: A double blind placebo-controlled study in children. Pediatr Infect Dis J. 1994;13:197-202.
8. Ravaud A, Chevreau C, Cany L, et al. Granulocyte-macrophage colony-stimulating factor in patients with neutropenic fever is potent after low-risk but not after high-risk neutropenic chemotherapy regimens: Results of a randomized phase III trial. J Clin Oncol. 1998;16:2950-6.
9. Mayordomo JI, Rivera F, Díaz-Puente MT, et al. Improving treatment of chemotherapy-induced neutropenic fever by administration of colony-stimulating factors. J Natl Cancer Inst. 1995;87:803-8.
10. Vellenga E, Uyl-de Groot CA, de Wit R, et al. Randomized placebo-controlled trial of granulocyte-macrophage colony-stimulating factor in patients with chemotherapy-related febrile neutropenia. J Clin Oncol. 1996;14:619-27.
11. Ozer H, Armitage JO, Bennet CL, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines-American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol. 2000;18:3558-85.
12. Hughes WT, Armstrong D, Bodey GP, et al. 1997 Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis. 1997;25:551-73.
13. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med. 1991;325:164-70.
14. Pettengell R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: A randomized controlled trial. Blood. 1992; 80:1430-6.
15. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer. 1993;29A:319-24.
16. Gerhartz HH, Engelhard M, Meusers P, et al. Randomized, double-blind, placebo-controlled, phase III study of recombinant human granulocyte-macrophage colony-stimulating factor as adjunct to induction treatment of high-grade malignant non-Hodgkin's lymphomas. Blood. 1993;82: 2329-39.
17. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. Am J Med. 2002;112:406-11.
18. Pettengell R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: A randomized controlled trial. Blood. 1992;80:1430-6.
19. Lyman GH. Guidelines of the National Comprehensive Cancer Network on the use of Myeloid Growth Factors with cancer chemotherapy: a review of evidence. JNCCN. 2005;3:557-71.
20. Kuderer NM, Crawford J, Dale CD, et al. Meta-analysis of prophylactic granulocyte colony-stimulating factor (G-CSF) in cancer patients receiving chemotherapy. J Clin Oncol. 2005;23(16S):S758.
21. Cosler LE, Eldar Lissai A, Dale DC, et al. Economic analysis of pegfilgastrim inpatients receiving cancer chemotherapy. J Clin Oncol. 2005;23 Suppl 16:S538.
22. Nichols CR, Fox EP, Roth BJ, et al. Incidence of neutropenic fever in patients treated with standard-dose combination chemotherapy for small-cell lung cancer and the cost impact of treatment with granulocyte colony-stimulating factor. J Clin Oncol. 1994;12:1245-50.
23. Hartmann LC, Tschetter LK, Habermann TM, et al. Granulocyte colony-stimulating factor in severe chemotherapy-induced afebrile neutropenia. N Engl J Med. 1997; 336:1776-80.
24. Stone RM, Berg DT, George SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. N Engl J Med. 1995; 332:1671-7.
25. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: A Southwest Oncology Group study. Blood. 1998;91: 3607-15.
26. Heil G, Hoelzer MA, Sanz MA, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. Blood. 1997; 90:4710-8.
27. Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte- macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: A study of the Eastern Cooperative Oncology Group (E1490). Blood. 1995;86:457-62.
28. Dombret H, Chastang C, Fenaux P, et al. A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. AML Cooperative Study Group. N Engl J Med. 1995;332: 1678-83.
29. Lowenberg B, Suciu S, Archimbaud E, et al. Use of recombinant GM-CSF during and after remission induction chemotherapy in patients aged 61 years and older with acute myeloid leukemia: final report of AML-11, a phase III randomized study of the Leukemia Cooperative Group of European Organisation for the Research

and Treatment of Cancer and the Dutch Belgian Hemato-Oncology Cooperative Group. Blood. 1997;90:2952-61.
30. Witz F, Sadoun A, Perrin M-C, et al. A placebo-controlled study of recombinant human granulocyte-macrophage colony-stimulating factor administered during and after induction treatment for de novo acute myelogenous leukemia in elderly patients. Blood. 1998;91:2722-30.
31. Schmetzer HM, Gerhartz HH, Wilmanns W. GM-CSF stimulates proliferation of clonal leukemic bone marrow cells in acute myeloid leukemia (AML) *in vitro*. Ann Hematol. 1999;78:449-55.
32. Birnbaum RA, O'Marcaigh A, Wardak Z, et al. Nf1 and Gmcsf interact in myeloid leukemogenesis. Mol Cell. 2000;5:189-95.
33. Bunn PA Jr, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol. 1995; 13:1632-41.
34. Clark OA, Lyman G, Castro AA, et al. Colony stimulating factors for chemotherapy induced febrile neutropenia: a meta-analysis of randomized trials. J Clin Oncol. 2005;23:4198-214.
35. Aviles A, Guzman R, García EL, et al. Results of a randomizaed trial of granulocyte colony-stimulating factor in patients with infection and severe granulocytopenia. Anticancer Drugs. 1996;7:592-7.
36. Johnson ML, Grimwood RE. Leukocyte colony-stimulating factors. A review of associated neutrophilic dermatoses and vasculitides. Arch Dermatol. 1994;130:77-81.
37. Antman KS, Griffin JD, Elias A, et al. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on chemotherapy-induced myelosuppression. N Engl J Med. 1988;319(10):593-8.
38. Brandt SJ, Peters WP, Atwater SK, et al. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on hematopoietic reconstitution after high-dose chemotherapy and autologous bone marrow transplantation. N Engl J Med. 1988; 318:869-76.
39. Glaspy JA, Baldwin GC, Robertson PA, et al. Therapy for neutropenia in hairy cell leukemia with recombinant human granulocyte colony-stimulating factor. Ann Intern Med. 1988;109:789-95.
40. Pietsch T, Buhrer C, Mempel K, et al. Blood mononuclear cells from patients with severe congenital neutropenia are capable of producing granulocyte colony-stimulating factor. Blood. 1991;77:1234-7.
41. Smith OP, Reeves BR, Kempski HM, et al. Kostmann's disease, recombinant HuG-CSF, monosomy 7 and MDS/AML. Br J Haematol. 1995;91:150-3.
42. Ohara A, Kojima S, Hamajima N, et al. Myelodysplastic syndrome and acute myelogenous leukemia as a late clonal complication in children with acquired aplastic anemia. Blood. 1997;90:1009-13.
43. Hashino S, Imamura M, Tanaka J, et al. Transformation of severe aplastic anemia into acute myeloblastic leukemia with monosomy 7. Ann Hematol. 1996;72:337-9.
44. Kaito K, Kobayashi M, Katayama T, et al. Long-term administration of G-CSF for aplastic anaemia is closely related to the early evolution of monosomy 7 MDS in adults. Br J Haematol. 1998;103:297-303.
45. Gribben JG, Devereux S, Thomas NS, et al. Development of antibodies to unprotected glycosylation sites on recombinant human GM-CSF. Lancet. 1990;335:434-7.
46. Koyanagi Y, O'Brien WA, Zhao JQ, et al. Cytokines alter production of HIV-1 from primary mononuclear phagocytes. Science. 1988;241:1673-5.
47. Wang J, Rodríguez G, Oravecz T, et al. Cytokine regulation of human immunodeficiency virus type 1 entry and replication in human monocytes/macrophages through modulation of CCR5 expression. J Virol. 1998;72:7642-7.