

Hematopoietic growth factors in the elderly

Review Article

Wassim Mchayleh*, Rajesh Sehgal, James Natale, Gurkamal Chatta

University of Pittsburgh Cancer Institute; Division of Hematology and Oncology.

***Correspondence:** Wassim Mchayleh MD, University of Pittsburgh Cancer Institute; Division of Hematology and Oncology, 5150 centre avenue, Pittsburgh PA 15232, USA; Tel: 412-648-6431; Fax: 412-745-2245; e-mail: Mchaylehw@upmc.edu

Key words: Elderly, Growth Factors, G-CSF, Erythropoietin

Abbreviations: acute myeloid leukemia, (AML); American Society of Clinical Oncology, (ASCO); bone marrow, (BM); end stage renal disease, (ESRD); erythropoietin, (EPO); granulocyte colony-stimulating factor, (G-CSF); Granulocyte-macrophage colony-stimulating factor, (GM-CSF); hematopoietic growth factors, (HGFs); hematopoietic stem cell, (HSC); hemoglobin, (Hgb); idiopathic thrombocytopenic purpura, (ITP); macrophage colony-stimulating factor, (M-CSF); mature leukocytes, (PMNs); megakaryocyte growth and differentiation factor, (MGDF); recombinant human G-CSF, (rhG-CSF); thrombopoietin, (TPO)

The authors have no relevant financial relationships.

Received: 13 May 2008; Revised: 17 June 2008

Accepted: 24 July 2008; electronically published: November 2008

Summary

The Hematopoietic System is subject to the aging process. This translates in a blunted response to Hematopoietic stress in the elderly population. The clinical use of Hematopoietic growth factors (HGFs) has helped transform the care of the elderly cancer patient. The indications for the use of hematopoietic growth factors in the elderly population are no different from the general population. In fact, given the increased susceptibility of the elderly cancer patient to treatment related morbidity and mortality, there may be even more compelling reason for the use of growth factors, to obviate complications of myelosuppression. We review the biology of aging and hematopoiesis, and the indications for the use of HGFs in the elderly.

I. Introduction

Senescence of the lympho-hematopoietic system is associated with an increased incidence of neoplasia, autoimmune diseases and infections (Ben-Yehuda and Weksler, 1992). In fact, cancer and infections constitute the top two causes of mortality in the population over 65 years (Saltzman and Peterson, 1987; Ben-Yehuda and Weksler, 1992). Myelosuppression, either in the context of cancer chemotherapy or as a consequence of severe infections, is a particularly vexing problem in the elderly (Begg and Carbone, 1983). Pancytopenia is a common manifestation of myelosuppression and negatively impacts the prognosis in elderly patients with cancer by i) increasing infection and bleeding-related morbidity, and ii) preventing the administration of optimal dosages of chemotherapy. Although the physiologic basis of this blunted hematopoietic response remains unclear (Baldwin Jr, 1988; Lipschitz et al, 1984), recent insights into the biology of hematopoiesis, together with the availability in the clinic of a number of hematopoietic growth factors (HGFs), has helped transform the care of the elderly

cancer patient. In this review, we will discuss: 1) the biology of aging and hematopoiesis, and 2) indications for the use of HGFs in the elderly.

II. Hematopoiesis and aging

The orderly development of the hematopoietic system and the maintenance of homeostasis require that a strict balance be maintained between self-renewal, differentiation, maturation, and cell loss (Metcalfe, 1988). Thus a small pool of stem cells can either self-renew or differentiate along one of several lineages to form mature leukocytes (PMNs), erythrocytes or platelets. One of the major questions with regard to the aging hematopoietic system is whether or not the pluripotent hematopoietic stem cell (HSC) has a finite replicative capacity. Evidence for a finite replicative capacity of the stem cell has been obtained both in *in vitro* long-term bone marrow (BM) cultures (Reincke et al, 1982), as well as in an elegant *in vivo* mouse model, where repeated total body irradiation was eventually able to induce hematopoietic exhaustion (Mauch et al, 1982). Thus, although finite, the lifespan of

HSCs, is thought to be well in excess of the potential life span of a species.

In humans, marrow progenitors can be enriched on the basis of surface markers expressed at sequential stages of maturation. Thus CD33 is found on most cells of the myeloid lineage in the marrow, and CD34 is expressed only by more primitive progenitors (1%-4% of the marrow cells). Precursors of myeloid colony-forming cells (pre-CFC) express CD34 and lack expression of CD33 and other antigens expressed by mature lymphoid and myeloid cells. Since CD34+ marrow cells can engraft and reconstitute hematopoiesis in lethally irradiated baboons and humans (Berenson et al, 1988, 1991), surface expression of CD34 on marrow and circulating cells, serves as a surrogate for stem cell function.

Recent studies in murine and human models, however, have indicated that CD34(-) HSC exist as well, which possess engraftment potential and distinct HSC characteristics. These studies challenge the dogma that HSC are uniformly found in the CD34(+) subset, and question whether primitive HSC are CD34(+) or CD34(-). The question of whether HSCs are CD34+ or CD34- remains unanswered (Engelhardt et al, 2002).

The aging process primarily affects stimulus-driven hematopoiesis, with little or no impact on the basal state (Baldwin Jr, 1988). The blunted hematopoietic response to stress has been ascribed to age-related deficits in marrow progenitor cell numbers, changes in the marrow microenvironment, decreased production of regulatory growth factors, or a combination of these mechanisms (Hirota et al, 1988; Lee et al, 1989). However, in a number of areas the data are conflicting. This is partly due to tremendous heterogeneity of the aging process and partly a result of the difficulty in separating the effects of age per se from the effects of occult diseases (Pinto et al, 2003). Data from inbred aging animals reveal consistent age-related defects, but human studies tend to show more variable results.

III. Aging and Hematopoietic Growth Factors

Proliferation and differentiation of progenitor cells to become mature blood cells requires intimate contact between stem cells, stromal cells and the extracellular matrix, and is mediated by the (HGFs) (Clark and Kamen, 1987; Metcalf, 1988; Bagby and Segal, 1995). The HGFs, on the basis of their action, are characterized either as multi-lineage hematopoietins, e.g., stem cell factor (SCF) (Williams et al, 1990; Broudy, 1997) or as lineage-restricted hematopoietins, e.g., granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), erythropoietin (EPO), and thrombopoietin (TPO) (Kaushansky et al, 1994; Spivak, 1998). In addition to the above growth factors, lymphohematopoiesis is modulated by an ever-expanding list of other cytokines, i.e., the interleukins.

Age-related deficits tend to be subtle and are of clinical import either when present cumulatively or under conditions of hematopoietic stress (Baldwin Jr, 1988; Pinto et al, 2003). Relatively few studies have specifically addressed the use of growth factors in the elderly

population. In a comprehensive review of the growth factor literature between 1987-1991, Shank Jr and Balducci, reported in 1992 that there was no age-related difference either in the mean time to response or in the level of absolute hematopoietic response at different doses of the growth factors in cancer clinical trials. In a prospective randomized study, the effects of recombinant human G-CSF (rhG-CSF) on the blood and marrow in 19 young and 19 healthy elderly volunteers were also evaluated (Chatta et al, 1994). No age-related compromise, either in the magnitude or in the timing of the PMN response to rhG-CSF, was found. PMN activation, both via opsonin receptor-dependent and receptor-independent pathways, was preserved with aging, and PMN kinetics were identical in the young and the elderly. Thus, the indications for the use of hematopoietic growth factors in the elderly population are no different from the general population and are briefly summarized (Table 1) (Repetto et al, 2003; Smith et al, 2006). In fact, given the increased susceptibility of the elderly cancer patient to treatment related morbidity and mortality, there may be even more compelling reason for the use of growth factors, to obviate complications of myelosuppression. Currently, of the various hematopoietic growth factors available clinically, the following may have special relevance for use in the elderly:

A. Granulocyte colony stimulating factor (Smith et al, 2006)

G-CSF is a 24kD glycoprotein promoting the growth and maturation of myeloid cells and in particular, the proliferation and differentiation of neutrophil progenitors both *in vitro* and *in vivo* (Demetri and Griffin, 1991; Lieschke and Burgess, 1992a,b). There are two recombinant forms of G-CSF currently available. Filgrastim (Neupogen®) is a non glycosylated, smaller molecule than its endogenous counterpart, but has the same biological activity (Osslund and Boone, 1994). Pegfilgrastim (Neulasta®) is pegylated formulation of G-CSF, allowing for an increased plasma half-life permitting once a chemotherapy cycle (every 14 to 21 days) administration as opposed to daily administration with non-pegylated G-CSF. Pegfilgrastim has shown a comparable safety and efficacy profile to filgrastim in three randomized clinical trials (Holmes et al, 2002; Green et al, 2003; Vose et al, 2003). Current indications for the use of G-CSF include:

1. Treatment of chemotherapy-related neutropenia

Crawford and colleagues in 1991 and Trillet-Lenoir and colleagues in 1993 were among the first to show that in patients receiving chemotherapy for lung cancer, concurrent administration of G-CSF (5 µg/kg/day) reduced the duration of neutropenia, decreased the incidence of febrile neutropenia, infections, antibiotic use, and hospitalization by approximately 50%. The current 2006 American Society of Clinical Oncology (ASCO) guidelines suggest reserving primary prophylaxis (ie, the use of hematopoietic growth factors with the first cycle and all subsequent cycles of chemotherapy) with HGF's

Table 1. Growth Factors in the Elderly

Growth Factor	Dosage and Administration	Indications
1-Granulocyte Colony-stimulating factor(G-CSF):		
1-Filgrastim(Neupogen®)	- Neutropenia: - 5mcg/kg/d sc (rounded to the nearest vial size), starting 24 to 72 hours after stopping chemotherapy and continuing until ANC \geq 1000 (shorter durations have been suggested) - PBSCT mobilization 10mcg/kd/d or 5-8mcg/kg/ bid have been used. Optimal duration and timing not established.	• Chemotherapy related neutropenia • Chronic and drug induced neutropenia • Peripheral blood stem cell transplantation • Myelodysplasia
2-Pegfilgrastim(Neulasta®):	- Neutropenia: - 6mg sc once per cycle (minimal 2 weeks between doses) - PBSCT mobilization: Ongoing studies.	
Growth Factor	Dosage and Administration	Indications
2-Erythropoietin(EPO) :		
1-RhEpo (Procrit®):	150 units/kg sc/IV three times weekly or 40,000-60,000 units weekly	• Renal disease with anemia • Anemia in cancer patients • Myelodysplasia
2-Darbepoetin (Aranesp®):	2.25 mcg/kg sc/IV weekly or 500mcg sc/IV every three weeks	
3-Granulocyte-Macrophage Colony-stimulating factor (GM-CSF):		
Sargamostim (Leukine®):	250-500 mcg/kd/d sc/IV (rounded to the nearest vial size), starting 24 to 72 hours after stopping chemotherapy and continuing until ANC \geq 1500/microL for two consecutive days.	• As for G-CSF • Vaccine adjuvant

administration for: a) high risk patients with an expected incidence of febrile neutropenia of $\geq 20\%$; b) patients at risk of increased complications from prolonged neutropenia (ie, elderly, poor performance status); and c) patients receiving dose dense chemotherapy (Smith et al, 2006). This is a change from ASCO's previous published guidelines which used a 40% incidence of febrile neutropenia as the trigger for primary prophylaxis (Vogel et al, 2005; Smith et al, 2006). In regards to patients at greater risk of complications due to prolonged neutropenia, aging (> 60-70yo) has been shown to be an independent risk factor for development of febrile neutropenia (Dees et al, 1984; Crivellari et al, 2000; Gelman and Taylor, 2004; Kim et al, 2007), as well as incurring a higher mortality rate from the complications of neutropenic infections (Armitage and Potter, 2003; Doorduyn et al, 2007; Gomez et al, 2007). Moreover, in two large retrospective reviews of lymphoma and breast cancer, age > 60-65 yo was an independent predictor of receiving less than 85% relative dose intensity (RDI-

defined as the delivered dose intensity over the standard dose intensity multiplied by 100) (Lyman et al, 2003; 2006). Thus, these studies have shown elderly cohorts to receive either lower doses or the same dose over a longer period of time than their younger counterparts. The significance of these dose reductions and delays, at least in the lymphoma and breast cancer populations, has been relevant reductions in overall survival (Kwak et al, 1990; Bonadonna et al, 1995). Based on these data, the latest ASCO guidelines have added recommendations for the use of HGF's in older patients. The recommendation includes the use of primary prophylaxis with HGF's in patients with lymphoma over the age of 65 receiving chemotherapy with a curative intent, regardless of the threshold risk of neutropenia based on the individual regimen used. The guidelines also comment on the practice of dose reducing or delaying in this population of lymphoma patients, stating this practice is no longer recommended. Instead the use of HGF's to maintain dose intensity (giving the planned dose at the planned time

interval), is a more reasonable strategy even in elderly patients receiving moderate-low myelosuppressive chemotherapy regimens.

2. Mobilization of PBSC for hematopoietic reconstitution (Fennelly et al, 1994; Tricot et al, 1995)

The use of G-CSF for the purpose of mobilizing stem cells into peripheral blood for subsequent use in autologous bone marrow transplantation is now established. In the elderly, hematopoietic support with PBSC may prove useful in the setting of high-dose chemotherapy for cancers resistant to standard chemotherapy, i.e., multiple myeloma and non-hodgkin's lymphoma. The dose of G-CSF for mobilizing PBSC ranges between 10-30 $\mu\text{g}/\text{kg}/\text{day}$. A study analyzed 150 patients with AML comparing CD34+ cells mobilization in patients older or younger than age 60. The successful mobilization rate ($>2 \times 10^6$ CD34+ cells/kg) was comparable between the two groups (87% vs. 80%, $p = 0.29$). In addition, no statistically significant difference was found in terms of either median number of CD34+ cells collected (Ferrara et al, 2007).

3. In hematological malignancies (Rowe et al, 1991; Dombret et al, 1994; Hiddemann et al, 1995; Stone et al, 2004)

Because of the presence of growth factor receptors on malignant myeloid cells, exacerbation of the underlying leukemia is a concern. However, in a number of studies, where G-CSF was used in the setting of myelodysplasia and acute myeloid leukemia (AML), there was no evidence of tumor stimulation. Most cases of AML occur in patients over the age of 60 years, usually in the setting of complex and unfavorable cytogenetic abnormalities. Compared with younger patients, the elderly have a lower response rate to induction therapy, a reduced probability of remaining in remission, and a lower cure rate. Furthermore, mortality in the cytopenic phase of treatment is also in the order of 30-40% in the elderly. The experience of three multi-center clinical trials using either G-CSF or GM-CSF in elderly patients with AML has been reported. The results of these studies are conflicting, and at this point no firm recommendations can be made. However, stimulation of the leukemic clone was not noted with either of the growth factors.

B. Granulocyte-macrophage colony-stimulating factor (GM-CSF) (Rowe et al, 1991; Nemunaitis et al, 2002; Witz et al, 2004)

GM-CSF, is a glycosylated peptide of 22kD, which has a broader range of cellular targets than G-CSF. The two forms of recombinant human GM-CSF currently in use are sargramostim (Leukine®), and molgramostim (non-glycosylated or E coli -derived). The effects of GM-CSF both in causing neutrophilia and in mobilizing PBSC are very similar to those of G-CSF. GM-CSF was first reported to enhance marrow recovery in the setting of autologous marrow transplantation for lymphoid malignancies. Currently GM-CSF is approved for use in

AML in the elderly. The use of GM-CSF as a vaccine adjuvant, in particular its ability to recruit dendritic cells to the site of injection is under investigation.

D. Erythropoietin (Rizzo et al, 1993; Spivak, 1998)

EPO has been in clinical use since 1985 for patients with end stage renal disease (ESRD). Erythropoiesis can be stimulated by exogenous administration of two FDA approved agents: the recombinant human erythropoietin (Epogen® or Procrit®), and darbepoetin alfa (Aranesp®). The latter is more heavily glycosylated and longer acting than the former. In the elderly, EPO may be indicated under the following circumstances:

1. ESRD on dialysis (Paganini and Miller, 1993; Locatelli et al, 2001)

The usual dose of EPO is 75-100 U/kg; administered three times per week during the last 5 minutes of dialysis. On this dose, 95% of patients reach the target hemoglobin ($> 11\text{gm}\%$ and $< 12\text{gm}\%$) in 10-12 weeks, have marked reduction in transfusion dependency, and have beneficial cardiac, neurovascular, immunologic, and psychosocial effects. For a normal response to EPO, the patient must have adequate iron stores and red cell folate. Although EPO is well tolerated, dialysis patients on EPO have a higher risk of hypertension, seizures, cerebrovascular disease, and thrombo-embolic episodes. Since the elderly are more prone to all the above diseases, older patients on EPO need to be monitored closely. The less frequent darbepoetin alfa dosing schedule of once weekly or once every two weeks, with the possibility of monthly dosing in some patients, offers many potential benefits to both patients and caregivers.

2. Anemia in cancer patients (Spivak, 2001, 2005)

Anemia is a common finding in patients with cancer. Usually it is multifactorial, being related to chronic disease, as well as cancer progression (marrow involvement) and cancer treatment (chemotherapy). Multiple studies have shown that patients with a hemoglobin (Hgb) level of 11 gm% benefit from epoetin therapy: they require fewer blood transfusions and have an enhanced sense of well-being. However Hgb levels consistently $> 12\text{gm}\%$, have been associated with vascular side-effects and a shorter life expectancy. More recent data on the effects of recombinant human erythropoietin and darbepoetin and tumor progression and thrombosis (Henke et al, 2003; Leyland-Jones et al, 2005; Bohlius et al, 2006; Wright et al, 2007; Unpublished results of the DAHANCA 10 Trial, 2007), have led to changes in the guidelines from the American Society of Clinical Oncology and the American Society of Hematology. This data clearly shows that targeting Hb concentrations of greater than 12 gm/dl increases the risk of thromboembolic events and potentially stimulates tumor growth. At this point, no conclusive evidence exists that these potential deleterious effects occur if current ASCO/ASH and FDA-approved dosing guidelines and

modifications are followed. The guidelines recommend use of epoetin as a treatment option for patients with chemotherapy-associated anemia with a Hgb concentration at or below 10 gm%. Subcutaneous epoetin can be used thrice weekly (150 IU/kg) for a minimum of 4 weeks. Alternatively, a weekly (40,000 IU/wk) dosing regimen is also reasonable. Current FDA-approved starting dose of darbepoetin is 2.25mcg/kg weekly or 500mcg every 3 weeks. However, the ASCO/ASH guidelines recognize alternative darbepoetin dosing as every two weeks at a dose of 200 mcg, or every 3 weeks at a dose of 300 to 400 mcg. Both agents should be titrated to a target hemoglobin concentration at or near 12 g/dL. Evidence from one randomized controlled trial supports use of epoetin for patients with anemia associated with low-risk myelodysplasia. Anemic patients with hematologic malignancies should be first treated with conventional therapy and monitored for a hematologic response, prior to considering the use of recombinant erythropoietic agents (Rizzo et al, 1993).

4. Thrombopoietin (Kaushansky et al, 1994; Archimbaud et al, 1999)

The gene for thrombopoietin was cloned 12 years ago, but the protein has not yet been approved for clinical use. It is likely that thrombopoietin will be useful for accelerating platelet recovery after intensive chemotherapy. It can augment the number of hematopoietic stem cells mobilized by G-CSF, increase the number of platelets available for apheresis from platelet donors, and stimulate platelet production in patients with myelodysplastic syndromes, idiopathic thrombocytopenic purpura (ITP), or liver disease. Thrombopoietin was initially called megakaryocyte growth and differentiation factor (MGDF) and was studied in several clinical trials prior to 1998. However its use was associated with the production of antibodies against MGDF that cross-reacted with endogenous thrombopoietin, causing severe thrombocytopenia (Li et al, 2000). This adverse event led to the abandonment of the use of MGDF and full-length forms of thrombopoietin as therapeutic proteins. Recent studies using small-molecules that mimic thrombopoietin in their ability to bind and stimulate the thrombopoietin receptor in ITP are ongoing (Bussel et al, 1984).

IV. Conclusions

The feverish pace of growth factor research and the arrival in the clinic of various growth factors have transformed the practice of modern day hematology-oncology. For the elderly cancer patient, there are now available newer, more effective and safer therapies with tremendous potential.

References

- Archimbaud E, Ottmann OG, Yin JA, Lechner K, Dombret H, Sanz MA, Heil G, Fenaux P, Brugger W, Barge A, O'Brien-Ewen C, Matcham J, Hoelzer D (1999) A randomized, double-blind, placebo-controlled study with pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) as an adjunct to chemotherapy for adults with de novo acute myeloid leukemia. **Blood** 94, 3694-3701.
- Armitage JO, Potter JF (1984) Aggressive chemotherapy for diffuse histiocytic lymphoma in the elderly: Increased complications with advancing age. **J Am Geriatr Soc** 32, 269-273.
- Bagby G, Segal G (1995) Growth factors and the control of hematopoiesis. In: Hoffman R, Benz EJ Jr, Shanttil SJ, et al, eds. Hematology Basic Principles and Practice. 2nd edition. New York, NY: Churchill Livingstone, 207.
- Baldwin JG Jr (1988) Hematopoietic function in the elderly. **Arch Intern Med** 148, 2544-2546.
- Begg CB, Carbone PP (1983) Clinical trials and drug toxicity in the elderly. The experience of the Eastern Cooperative Oncology Group. **Cancer** 52, 1986-1992.
- Ben-Yehuda A, Weksler ME (1992) Host resistance and the immune system. **Clin Geriatr Med** 8, 701-711.
- Berenson RJ, Andrews RG, Bensinger WI, Kalamasz D, Knitter G, Buckner CD, Bernstein ID (1988) Antigen CD34+ marrow cells engraft lethally irradiated baboons. **J Clin Invest** 81, 951-955.
- Berenson RJ, Bensinger WI, Hill RS, Andrews RG, Garcia-Lopez J, Kalamasz DF, Still BJ, Spitzer G, Buckner CD, Bernstein ID (1991) Engraftment after infusion of CD34+ marrow cells in patients with breast cancer or neuroblastoma. **Blood** 77, 1717-1722.
- Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, Trelle S, Weingart O, Bayliss S, Djulbegovic B, Bennett CL, Langensiepen S, Hyde C, Engert A (2006) Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. **J Natl Cancer Inst** 98, 708.
- Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C (1995) Adjuvant Cyclophosphamide, Methotrexate and fluorouracil in node-positive breast cancer. **N Engl J Med** 332, 901-906.
- Broudy VC (1997) Stem cell factor and hematopoiesis. **Blood** 90, 1345-1364.
- Bussel J, Kuter D, George J, Aledort L, Lichtin A, Lyons R, Nieva J, Wasser J, Bourgeois E, Kappers-Klunne M, Lefrere M, Schipperus M, Kelly R, Christal J, Guo M, Nichol J (2005) Long-term dosing of AMG 531 is effective and well tolerated in thrombocytopenic patients with immune thrombocytopenic purpura (Abst 511). **Blood** 106, 68a.
- Chatta GS, Price TH, Allen RC, Dale DC (1994) Effects of in vivo recombinant methionyl human granulocyte colony-stimulating factor on the neutrophil response and peripheral blood colony-forming cells in healthy young and elderly adult volunteers. **Blood** 84, 2923-2929.
- Clark SC, Kamen R (1987) The human hematopoietic colony-stimulating factors. **Science** 236, 1229-1237
- Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, Kris M, Grous J, Picozzi V, Rausch G (1991) Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. **N Engl J Med** 325, 164-170.
- Crivellari D, Bonetti M, Castiglione-Gertsch M, Gelber RD, Rudenstam CM, Thürlimann B, Price KN, Coates AS, Hüry C, Bernhard J, Lindtner J, Collins J, Senn HJ, Cavalli F, Forbes J, Gudgeon A, Simoncini E, Cortes-Funes H, Veronesi A, Fey M, Goldhirsch A (2000) Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: The International Breast Cancer Study Group Trial VII. **J Clin Oncol** 18, 1412-1422.
- Dees EC, O'Reilly S, Goodman SN, Sartorius S, Levine MA, Jones RJ, Grochow LB, Donehower RC, Fetting JH (2000) A prospective pharmacologic evaluation of age-related toxicity

- of adjuvant chemotherapy in women with breast cancer. **Cancer Invest** 18, 521-529.
- Demetri GD, Griffin JD (1991) Granulocyte colony-stimulating factor and its receptor. **Blood** 78, 2791-2808.
- Dombret H, Chastang C, Fenaux P, Reiffers J, Bordessoule D, Bouabdallah R, Mandelli F, Ferrant A, Auzanneau G, Tilly H, Yver A, Degos L (1995) 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** 332, 1678-1683.
- Doorduijn JK, van der Holt B, van Imhoff GW, van der Hem KG, Kramer MH, van Oers MH, Ossenkoppele GJ, Schaafsma MR, Verdonck LF, Verhoef GE, Steijaert MM, Buijt I, Uyl-de Groot CA, van Agthoven M, Mulder AH, Sonneveld P (2003) CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. **J Clin Oncol** 21, 3041-50.
- Fennelly D, Vahdat L, Schneider J, Reich L, Hamilton N, Hakes T, Raptis G, Wasserheit C, Kritz A, Gulati S, Markman M, Hoskins W, Norton L, Crown J (1994) High-intensity chemotherapy with peripheral blood progenitor cell support. **Semin Oncol** 21(Suppl2), 21-26, 58.
- Ferrara F, Viola A, Copia C, Falco C, D'Elia R, Tambaro FP, Correale P, D'Amico MR, Vicari L, Palmieri S (2007) Age has no influence on mobilization of peripheral blood stem cells in acute myeloid leukemia. **Hematol Oncol.** 25, 84-9.
- Fosså SD, Kaye SB, Mead GM, Cullen M, de Wit R, Bodrogi I, van Groeningen CJ, De Mulder PH, Stenning S, Lallemand E, De Prijck L, Collette L (1998) Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. **J Clin Oncol** 16, 716-724.
- Gelman RS, Taylor SG (1984) Cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: The elimination of age trends in toxicity by using doses based on creatinine clearance. **J Clin Oncol** 2, 1404-1413.
- Gómez H, Mas L, Casanova L, Pen DL, Santillana S, Valdivia S, Otero J, Rodriguez W, Carracedo C, Vallejos C (1998) Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: Identification of two age subgroups with differing hematologic toxicity. **J Clin Oncol.** 16, 2352-2358.
- Green MD, Koelbl H, Baselga J, Galid A, Guillem V, Gascon P, Siena S, Lalisang RI, Samonigg H, Clemens MR, Zani V, Liang BC, Renwick J, Piccart MJ; International Pegfilgrastim 749 Study Group (2003) A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. **Ann Oncol** 14, 29-35.
- Henke M, Laszig R, Rube C, Schäfer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C, Frommhold H (2003) Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. **Lancet** 362, 1255-1260.
- Heuser M, Ganser A (2005) Colony-stimulating factors in the management of neutropenia and its complications. **Ann Hematol** 84, 697-708.
- Hiddemann W, Wörmann B, Reuter C, Schleyer E, Zühlendorf M, Böckmann A, Büchner T (1994) New perspectives in the treatment of acute myeloid leukemia by hematopoietic growth factors. **Semin Oncol** 21(6 Suppl16), 33-38.
- Hirota Y, Okamura S, Kimura N, Shibuya T, Niho Y (1988) Haematopoiesis in the aged as studied by in vitro colony assay. **Eur J Haematol** 40, 83-90.
- Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, Glaspy J, Moore M, Meza L, Wiznitzer I, Neumann TA, Hill LR, Liang BC (2002) Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. **J Clin Oncol** 20, 727-731.
- Kaushansky K, Lok S, Holly RD, Broudy VC, Lin N, Bailey MC, Forstrom JW, Buddle MM, Oort PJ, Hagen FS, Roth GJ, Papayannopoulou T, Foster DC (1994) Promotion of megakaryocyte progenitor expansion and differentiation by the c-Mpl ligand thrombopoietin. **Nature** 369, 568-571.
- Kaushansky K (2006) Lineage-specific hematopoietic growth factors (abst 2411). **N Engl J Med** 354, 2034-2045.
- Kim YJ, Rubenstein EB, Rolston KV, Elting L, Paesmans M, Talcott J, Klastersky J (2000) Colony-stimulating factors (CSFs) may reduce complications and death in solid tumor patients with fever and neutropenia (Abst 2411). **Proc AM Soc Clin Oncol** 19.
- Kwak LW, Halpern J, Olshen RA, Horning SJ (1990) Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: Results of a tree-structured survival analysis. **J Clin Oncol** 8, 963-977.
- Lee MA, Segal GM, Bagby GC (1989) The hematopoietic microenvironment in the elderly: Defects in IL-1-induced CSF expression in vitro. **Exp Hematol** 17, 952-956.
- Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X, Vercammen E (2005) Maintaining Normal Hemoglobin Levels with Epoetin alfa in Mainly Nonanemic Patients with Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. **J Clin Oncol.** 23, 5960-5972.
- Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, Kuter DJ (2001) Thrombocytopenia caused by the development of antibodies to thrombopoietin. **Blood** 98, 3241-3248.
- Lieschke GJ, Burgess AW (1992a) Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor (2). **N Engl J Med** 327, 99-106.
- Lieschke GJ, Burgess AW (1992b) Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. **N Engl J Med** 327, 28-35.
- Lipschitz DA, Udupa KB, Milton KY, Thompson CO (1984) Effect of age on hematopoiesis in man. **Blood** 63, 502-509.
- Locatelli F, Olivares J, Walker R, Wilkie M, Jenkins B, Dewey C, Gray SJ; European/Australian NESP 980202 Study Group (2001) Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. **Kidney Int** 60, 741-747.
- Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI (2004) Incidence and Predictors of Low Chemotherapy Dose-Intensity in Aggressive Non-Hodgkin's Lymphoma: A Nationwide Study. **J Clin Oncol.** 22, 4302-4311.
- Lyman GH, Dale DC, Crawford J (2003) Incidence and Predictors of Low Dose-Intensity in Adjuvant Breast Cancer Chemotherapy: A Nationwide Study of Community Practices. **J Clin Oncol.** 21, 4524-4531.
- Mauch P, Botnick LE, Hannon EC, Obbagy J, Hellman S (1982) Decline in bone marrow proliferative capacity as a function of age. **Blood** 60, 245-252.

- Metcalfe D (1988) *The Molecular Control of Blood Cells*. Cambridge, MA; Harvard University Press.
- Nemunaitis J, Rabinowe SN, Singer JW, Bierman PJ, Vose JM, Freedman AS, Onetto N, Gillis S, Oette D, Gold M, Buckner CD, Hansen JA, Ritz J, Appelbaum FR, Armitage JO, Nadler LM (1991) Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. *N Engl J Med* 324, 1773-1778.
- Nemunaitis J, Rosenfeld C (1993) Mobilization of peripheral stem cells for transplantation. *J Hematother* 2, 351-355.
- Ohno R, Tomonaga M, Kobayashi T, Kanamaru A, Shirakawa S, Masaoka T, Omine M, Oh H, Nomura T, Sakai Y, Hirano M, Yokomaku S, Nakayama S, Yoshida Y (1990) Effect of granulocyte colony-stimulating factor after intensive induction therapy in relapsed or refractory acute leukemia. *N Engl J Med* 323, 871-877.
- Osslund T, Boone T (1994) Biochemistry and structure of filgrastim (R-met-HuG-CSF). In: Morstyn G, Dexter TM, eds. *Filgrastim (r-metHuG-CSF) in Clinical Practice*. New York, NY: Marcel Dekker, Inc., pp. 23-31.
- Paganini EP, Miller T (1993) Erythropoietin therapy in renal failure. *Adv Intern Med* 38, 223-243.
- Pinto A, De Filippi R, Frigeri F, Corazzelli G, Normanno N (2003) Aging and the hemopoietic system. *Crit Rev Oncol Hematol* 48 (Suppl), S3-S12.
- Reinke U, Hannon EC, Rosenblatt M, Hellman S (1982) Proliferative capacity of murine hematopoietic stem cells in vitro. *Science* 215, 1619-1622.
- Repetto L, Biganzoli L, Koehne CH, Luebbe AS, Soubeyran P, Tjan-Heijnen VC, Aapro MS (2003) EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer* 39, 2264-2272.
- Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, Djulbegovic B, Goode MJ, Jakubowski AA, Lee SJ, Miller CB, Rarick MU, Regan DH, Browman GP, Gordon MS; American Society of Clinical Oncology; American Society of Hematology (2002) Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *Blood* 100, 2303-2320.
- Rowe JM, Andersen JW, Mazza JJ, Bennett JM, Pianta E, Hayes FA, Oette D, Cassileth PA, Stadtmauer EA, Wiernik PH (1995) 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* 86, 457-462.
- Saltzman RL, Peterson PK (1987) Immunodeficiency of the elderly. *Rev Infect Dis* 9, 1127-1139.
- Shank WA Jr, Balducci L (1992) Recombinant hemopoietic growth factors: Comparative hemopoietic response in younger and older subjects. *J Am Geriatr Soc* 40, 151-154.
- Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC (2006) 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. *J Clin Oncol* 24, 3187-3205.
- Spivak JL (2005a) Anemia in the elderly: Time for new blood in old vessels? *Arch Intern Med* 165, 2187-2189.
- Spivak JL (2005b) The anaemia of cancer: Death by a thousand cuts. *Nat Rev Cancer* 5, 543-555.
- Spivak JL (1998) The biology and clinical applications of recombinant erythropoietin. *Semin Oncol* 25 (3 Suppl 7), 7-11.
- Stone RM, Berg DT, George SL, Dodge RK, Paciucci PA, Schulman P, Lee EJ, Moore JO, Powell BL, Schiffer CA (1995) Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. *N Engl J Med* 332, 1671-1677.
- Tricot G, Jagannath S, Vesole D, Nelson J, Tindle S, Miller L, Cheson B, Crowley J, Barlogie B (1995) Peripheral blood stem cell transplants for multiple myeloma: Identification of favorable variables for rapid engraftment in 225 patients. *Blood* 85, 588-596.
- Trillet-Lenoir V, Green J, Manegold C, Von Pawel J, Gatzemeier U, Lebeau B, Depierre A, Johnson P, Decoster G, Tomita D, Ewen C (1993) Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 29A, 319-324.
- Unpublished results of the DAHANCA 10 Trial (2007) Data available at: http://frejacms.au.dk/dahanca/get_media_file.php?medlaid=125, accessed March 30, 2007.
- Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL, Neumann TA, Schwartzberg LS (2005) First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol* 23, 1178-1184.
- Vose JM, Crump M, Lazarus H, Emmanouilides C, Schenkein D, Moore J, Frankel S, Flinn I, Lovelace W, Hackett J, Liang BC (2003) Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. *J Clin Oncol* 21, 514-519.
- Williams DE, Eisenman J, Baird A, Rauch C, Van Ness K, March CJ, Park LS, Martin U, Mochizuki DY, Boswell HS, Burgess GS, Cosman D, Lyman SD (1990) Identification of a ligand for the c-kit proto-oncogene. *Cell* 63, 167-174.
- Witz F, Harousseau JL, Guilhot F, Cahn JY, Witz B, Loos C, Chevalier MP, Guibon O, Berthaud P, Lioure B; Groupe Ouest Est Leucémies Aiguës Myéloblastiques (2004) Priming with GM-CSF for acute myelogenous leukemia (AML): GOELAM data. *Ann Hematol* 83 (Suppl1), S55-S57.
- Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C, Szechtman B, Roa W, Mulroy L, Rudinkas L, Gagnon B, Okawara GS, Levine MN (2007) Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non-Small Cell Lung Cancer with Disease-Related Anemia. *J Clin Oncol* 25, 1027-1032.

