

HEMATOPOIETIC GROWTH FACTORS AND ACUTE MYELOID LEUKEMIA

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Receptors for a variety of cytokines, including c-kit ligand, interleukin-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) and thrombopoietin are expressed on acute myeloid leukemia (AML) cells at physiological densities in most patients.⁽²⁾ These receptors are of high affinity. When the ligands are added to cultures of AML cells, induction of metabolic and cell cycle activation appears. In some cases AML cells may mature towards terminally differentiated cells in response to cytokine stimulation. When AML cells stimulated with hematopoietic growth factors are subjected to chemotherapy *in vitro*, cell killing may be considerably enhanced.⁽¹⁾ These observations have been a reason for applying hematopoietic growth factors in the treatment of patients with AML. Thus, hematopoietic growth factors have been applied not only to accelerate hematopoietic regeneration following chemotherapy or hematopoietic stem cell transplantation to reduce morbidity and mortality, they have also been applied to prime AML cells for chemotherapy and to enhance the antileukemic efficacy of treatment. In selected conditions hematopoietic growth factors might also be applied to induce terminal maturation in leukemic blasts and overcome the maturation arrest. This may result in the extinction of the leukemic cell clone.

The Use of Hematopoietic Growth Factors to Prevent Infectious Complications During Neutropenia

The probability of infection and the risk of infectious mortality correlate directly with the severity and duration of neutropenia. G-CSF and GM-CSF may stimulate the survival, proliferation and maturation of myeloid precursor cells and activate granulocyte function. In a variety of studies G-CSF or GM-CSF have been administered to patients with AML after the completion of induction chemotherapy and continued until granulocyte recovery. Four randomized studies have been conducted in previously untreated patients⁽⁴⁻⁷⁾ and one study in patients with relapsed or refractory AML (see Table 1).⁽³⁾ These studies were carried out in a relatively aged population of patients. The median age of each of these studies ranged between 49 and 70 years. In two studies GM-CSF was used; in the other three studies G-CSF was evaluated. In all five studies the application of G-CSF or GM-CSF resulted in a reduction in the duration of severe neutropenia ($0.5 \times 10^9/l$), although it varied from 2 to 12 days. In two of these studies patients on the G-CSF treatment showed an improved complete remission rate.^(6,7) In none of the studies were benefits apparent with respect to the duration of hospitalization, the number of infections, the use of antibiotics. Only one study showed an improvement of survival (Table 1).

Table 1. Results of randomized studies of GM-CSF and G-CSF post induction chemotherapy

Ref., yr .of publ.	Age (median)	Number of cases of the two arms		Chemo- therapyneutrophils	Days towards 0.5 x 10 ⁹ /l
Ohno 1990	13-69 (49)	G-CSF none	48 50	MBE	20 28 p=0.0002
Rowe 1995	55-70 (64)	GM-CSF placebo	57 57	DA	13 17 p=0.001
Stone 1995	> 60 (69)	GM-CSF placebo	193 195	DA	15 17 p=0.02
Dombret 1995	> 65 (70)	G-CSF placebo	88 85	DA	NR NR p=0.007
Godwin 1995	> 55 (67)	G-CSF placebo	93 100	DA	NR NR

Ref., yr.of publ.	Days towards neutrophilis 1.0 x 10 ⁹ /l	CR	Mortality (%)		Resistant Disease (%)	Survival
Ohno 1990	22 34 p=0.0002		50 36	4 12	60 54	NR NR
Rowe 1995	14 21 p=0.001		60 44	6 15	NR NR	10.6 mo 4.8 mo (median)p=0.048
Stone 1995	NR NR		51 54	27 23	22 23	0.7yr 0.9 yr (median)
Dom- bret 1995	21 27 p=0.002		70 47	15 20	15 33 p=0.007	45% 40% (at 1 yr)

God-	NR	42	17	NR	5 mo
win	NR	49	14	NR	9 mo
1995		p=0.002			(median)

Enhancement of Chemotherapy Efficacy by Hematopoietic Growth Factor Priming

Three randomized studies of previously untreated patients and one study in patients with refractory or relapsed AML have been carried out in which GM-CSF or G-CSF was also applied concomitantly with chemotherapy. All these studies have been carried out with GM-CSF. These studies as yet do not provide evidence for an increased efficacy of chemotherapy in the context of hematopoietic growth factor priming, a reduced relapse rate or an improved survival.⁽¹³⁾ A negative effect on treatment outcome has not become apparent either.

The Use of Hematopoietic Growth Factors for Induction of Maturation in Patients with AML

In certain situations leukemic cells can be provoked to terminal differentiation.⁽⁹⁻¹⁰⁾ In animal models G-CSF stimulation of leukemias in vivo may induce a loss of clonogenic potential and extinction of the leukemia.⁽⁸⁾ This notion has been substantiated most prominently in clinical practice in acute promyelocytic leukemia where all-trans retinoic acid may induce terminal maturation in vitro and in vivo and also induce complete responses in clinical practice. These leukemias are characterized by the t(15;17) translocation that involves the PML-gene on chromosome 15 and the retinoic acid receptor alpha gene on chromosome 17. In AML with the t(8;21), G-CSF and IL-5 in culture have been shown to induce morphological maturation towards neutrophils and eosinophils, respectively.⁽¹¹⁾ These factors have not been evaluated clinically, but future studies in well-defined subsets of patients with AML to address the potential value of maturation induction as part of new treatment strategies deserve to be carried out.

Perspectives

Clearly additional studies appear warranted to evaluate a variety of conditions of hematopoietic growth factor therapy in distinct subsets of patients with AML. For instance, differentiation induction treatment of the AML t(8;21) subtype with G-CSF remains an appealing option. Autologous marrow transplantation offers a treatment modality that is currently used in patients with AML up to 60 years of age who have no suitable HLA-matched donor. Autologous marrow transplantation often cannot be carried out because of the harvest of an inadequate marrow graft. In addition, it is frequently associated with a delay of hematopoietic regeneration. The transplantation of peripheral blood progenitor cells following hematopoietic growth factor mobilization might offer a vital alternative to the use of autologous marrow grafts in patients with AML.⁽¹²⁾ The feasibility of PBPC collection is currently a subject of intense study.

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