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GM-CSF in Marrow Transplantation

Karen H. Antman

Bone marrow transplantation (BMT) is being increasingly used in a wide variety of diseases. During the period of re-engraftment the patient is particularly susceptible to a number of opportunistic infections which can radically affect acute morbidity and mortality. Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) has been shown to mobilise haemopoietic progenitor cells for use after high-dose therapy, to enhance myeloid engraftment and stimulate mature monocytes/macrophages and neutrophils. Evidence is emerging that GM-CSF may be useful in BMT. A review of clinical trials in patients receiving BMT has revealed that the administration of rhGM-CSF significantly reduces the duration to re-engraftment, number of antibiotic treatment days, and the period of hospitalisation. Thus, rhGM-CSF appears to be a useful adjunct to BMT.
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INTRODUCTION

BONE MARROW TRANSPLANTATION has been utilised in a wide variety of diseases including refractory or relapsing haematologic disorders, carcinoma of the breast, paediatric sarcoma, retinoblastoma, melanoma and neuroblastoma [1-6]. There are a number of factors which affect the outcome of the transplant, however, the ultimate survival of the patient relates to the status of the tumour (refractory, relapsing) graft-versus-host disease, opportunistic infections or interstitial pneumonia. Syngeneic or autologous marrow appears to avoid some of these problems. Regardless of the source of bone marrow, the acute morbidity and mortality relate to the incidence of bleeding and infection secondary to the period of thrombocytopenia and granulocytopenia during recovery which may take 6 weeks or more.

Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF), administered during the period of neutropenia, significantly shortens time to myeloid engraftment. This review will summarise those studies undertaken to date to investigate the role of rhGM-CSF in marrow transplantation.

HIGH-DOSE THERAPY WITH rhGM-CSF AND STEM CELL SUPPORT

There is a close correlation between the dose of many chemotherapeutic agents (particularly alkylating agents for which kinetic resistance does not apply) and tumour cytotoxicity in many laboratory models and in clinical studies. Myelosuppression is the dose-limiting toxicity for many chemotherapy regimens and thus optimum response cannot be achieved within acceptable levels of myelosuppression. The concept of removal and storage of sufficient numbers of haematopoietic stem cells to re-establish normal marrow function is well established, both in animal models and in many human trials. In tumours such as lymphomas and Hodgkin's disease, high-dose chemotherapy with autologous marrow support appears to result in prolonged disease-free survival compared to treatment with standard chemotherapy regimens for failing standard therapy.

The major morbidity of high-dose chemotherapy results from suppression of granulopoiesis. The incidence of bacterial and fungal infection correlates with both duration and severity of neutropenia. More rapid haematological reconstitution would substantially reduce mortality, morbidity and the expense of high-dose therapy.

In studies of time to recovery of granulopoiesis in patients administered rhGM-CSF after marrow reinfusion [7-16] (Table 1), compared with historical controls, there were modest statistically significantly decreased times to re-engraftment in all but one, with fewer episodes of bacteraemia or organ toxicity in the majority of studies. In the negative study [10], which used purged marrows, there was no enhanced recovery overall but the authors noted that those patients who had the highest levels of granulocyte-macrophage colony-forming units (CFU-GM) reinfused had a shorter time to recovery than expected. Platelet recovery in these studies was inconsistently affected. Significant shortening of time to polymorphonuclear neutrophil counts (PMN) >500, >20000 platelets and duration of hospitalisation were reported in some series. Variability appears considerably related to prior chemotherapy.

There are several studies when rhGM-CSF was administered to patients with poor graft function after autologous or allogenic bone marrow. One-half to two-thirds of patients are reported to benefit from rhGM-CSF. Also striking was the poor response of patients who had received purged marrow (Table 1) [17-19].

In randomised placebo-controlled trials of rhGM-CSF after bone marrow transplant (Table 1) [20-26], only one study shows no significant difference in duration of neutropenia <500, although there was a significant difference in recovery of neutrophils to >1000 [20]. Thus, in all studies there was more rapid recovery in the arm receiving rhGM-CSF.

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Table 1. CSF studies in bone marrow transplantation

Study/reference	Institution	No. of patients	Days to PMN >500 cells/μl	
Historical controls			rhGM-CSF	Control
Brandt [7]	Duke	19	16	19
Nemunaitis [8]	Seattle	15	14	25
Nemunaitis [9]	Seattle	12	11	
Blazar [10]	Minnesota	25	24	23
Herremann [11, 12]	Mainz	28	Significant difference	
Link [13]	Hannover	11	14	20
Linkesch [14]	Vienna	4	15	24
Lazarus [15]	Cleveland	12	14	22
Devereaux [16]	London	12	18	25
Poor graft function			Response	
			Yes	No
Klingemann [17]	Vancouver	9	6	3
Nemunaitis [18]	Seattle	37*	21	16*
Vose [19]	Nebraska	12	9	3
Randomised trials			Days to ANC >500 μl	
			rhGM-CSF	Placebo
Nemunaitis [20, 21]	Seattle	42	15†	17
Armitage [21]	Nebraska	40	23	29
Rabinowe [21, 22]	DFCI	47	20	27
Gorin [23]	Paris	88	14	21
Link [24]	European Cooperative Trust	79	15	28
Michon [25]	Paris	21	18	26
Philip [26]				

*Including 7/7 purged marrows. Significant improvement in all cases except†. ANC = Absolute neutrophil count.
PMN, Polymorphonuclear neutrophils.

A few authors are currently attempting to culture marrow for transplant with cytokines in an effort to achieve earlier engraftment [27, 28]. After 3 days incubation, rhGM-CSF produced an eight-fold enhancement of CFU-GM over controls; co-incubation with interleukin (IL)-3 had an additive effect [29].

rhGM-CSF MOBILISED PERIPHERAL BLOOD PROGENITOR CELLS

There is no clear understanding of why peripheral blood contains progenitor cells (PBPC), or of their regulation. Stem cells collected from the peripheral blood of laboratory animals by cytophoresis successfully reconstitute myelopoiesis following marrow-lethal treatment [30, 31]. PBPC appear lymphoid under the microscope, express CD34 differentiation markers and can be quantitated by either CFU-GM assays or via flow cytometry [32].

CLINICAL STUDIES

Leukapheresis

The concentration of true "stem" cells is not measurable in the human (because of the lack of an assay), but it is common practice to measure the number of progenitor cells committed to myeloid (granulocyte/monocyte) and to erythroid maturation (measured as CFU-GM and erythroid burst-forming units (BFU-E), respectively). Leukapheresis is an outpatient procedure similar to platelet donation. Marrow donation currently involves hospitalisation, general anaesthesia and aspiration of 500-1000 ml of marrow from pelvic bones. Using the leukapheresis technique, adequate numbers of stem cells may be collected from patients with hemipelvectomies, tumour involving the pelvic bones or after pelvic irradiation. Granulocyte reconstitution may be faster, possibly due to reinfusion of larger numbers of committed mononuclear cells. Recovery of immune function appears faster and more complete possibly due to increased numbers of reinfused lymphocytes. A consistent feature of PBPC compared with bone marrow transplants has been rapid granulocyte reconstitution (10-16 days to >500 μl), and equivalent rates of platelet recovery (19-25 days).

Methods of increasing CFU-GM yields during leukapheresis

Previous efforts to augment circulating progenitor cell numbers have had limited success. Richman *et al.* [33] first observed that 9 of 14 patients given cyclophosphamide and doxorubicin had a significantly increased concentration of peripheral blood CFU-GM at the time of leucocyte recovery [34-37]. Nonetheless, between seven and 10 leukapheresis procedures are required for adequate stem cell collection. However, the average of eight leukapheresis treatments required per patient strains blood bank and cryopreservation resources and delays therapy for 3 weeks. Thus, PBPC reinfusion was not practical as a routine source of stem cells. One interesting technique currently under investigation is to positively select CD34 cells using monoclonal antibody bound to the inner surface of a collecting device [38].

Effect of rhGM-CSF on PBPC

Augmentation of PBPC by rhGM-CSF may facilitate collection of adequate numbers of PBPC with fewer leukapheresis procedures, thereby enhancing the feasibility of PBPC autografting.

The use of rhGM-CSF, with or without chemotherapy, to augment progenitor cell numbers prior to pheresis could, theoretically, reduce the number of required phereses (and aliquots frozen) to one or two per patient (Table 2) [39-44].

DANA FARBER CANCER INSTITUTE/BETH ISRAEL HOSPITAL STUDIES

These studies were carried out in women with metastatic breast cancer and in patients with solid tumours. The former were sequential trials in metastatic breast cancer patients responding to conventional dose therapy, high-dose cyclophosphamide, thiotepa and carboplatin, who were treated with marrow only or PBPC only. Circulating haematopoietic stem cells, collected in a total of four 2-h phereses, were mobilised by rhGM-CSF at a dose of 10 μg/kg by continuous intravenous infusion after two cycles of standard dose doxorubicin and 5-fluorouracil. The patients with solid tumours had been treated with high dose ifosfamide, carboplatin and etoposide. Those who could stay in the Boston area for a week received subcutaneous rhGM-CSF 5 μg/kg twice daily on days 1-7 after marrow harvest. In these patients, PBPC were

Table 2. Studies of mobilisation of peripheral blood progenitor cells after rhGM-CSF with or without chemotherapy

Reference	Institution	No. of patients	Cytokine alone (fold increase/ml)		Cytokine + chemotherapy (fold increase/ml)	
			CFU-GM	BFU-E	CFU-GM	BFU-E
Socinski *et al.* [39]	DFCI	12	18.0	8.0	63	17
Haas *et al.* [40]	Adelaide	11	8.5			
Villeval *et al.* [41]	Melbourne	37	8.4	3.3		
Siena *et al.* [42], Ravagnani *et al.* [43,44]	Milan	36	5.0			

Table 3. Results of rhGM-CSF stem-cell augmentation: bone marrow alone versus PBPC ± bone marrow (BM)

	Cyclophosphamide, thiotepa and carboplatin for breast cancer			Ifosfamide, etoposide and carboplatin for solid tumours		
	BM alone	*P*	PBPC alone	BM	*P*	PBPC + BM
No. of patients	29		15	13		13
No of leukaphereses	0		4	0		2
Days from reinfusion to						
ANC > 500 µl	21 (21-51)	*	14 (10-57)	25 (17-31)	*	17 (12-27)
Platelets > 20000 µl	24 (7-83)		12 (8-134)	18 (12-29)	*	16 (10-26)
Platelet units required	105 (11-1350)	*	22 (10-237)			
Platelets < 50000 µl on day 50	3		4	–		
Hospital days	32 (21-112)	*	24 (19-34)	35 (28-41)	*	27 (20-48)
Toxic deaths	1 (sepsis)		1 (cardiac)	2 (sepsis, bleed)		0
Sepsis/pneumonias	8		2	9		8

* Significant differences. Values are expressed as median (range). BM, bone marrow.

Table 4. Engraftment after use of cytokine-enhanced collection of PBPC with or without marrow or rhGM-CSF

Reference	No. of patients	Source of stem cells	Tumour	rhGM-CSF after reinfusion	Days to recovery	
					ANC > 500 µl	Platelets > 20000 µl
Gianni *et al.* [45-48]	7	PB+BM	Breast, lymphoma	No	9	11
Peters *et al.* [49]	17	PB+BM	Breast	Yes	–	–
Korbling *et al.* [50]	11	PB	Hodgkin's disease	No	20	38
Pileri *et al.* [51]	2	PB	Myeloma	No	–	–
Elias *et al.* [52]	15	PB	Breast	No	14	12
Mazanet *et al.* [53]	3	PB+BM	Solid tumours	No	20	38

PB, peripheral blood; BM, bone marrow.

harvested during 2-h phereses on days 5 and 7; both marrow and PBPC were reinfused. All other patients received marrow alone. No purging of PBPC or bone marrow was performed. No rhGM-CSF was administered after marrow or PBPC reinfusion (Table 3). Compared to marrow alone, PBPC support with or without marrow significantly reduced the median days to absolute neutrophil count (ANC) >500 µl, platelets >20000 µl, total hospital days and number of platelet transfusions, in both groups of patients (Table 4) [45-53].

CONCLUSIONS

In conclusion, rhGM-CSF enhances the recovery and function of circulating white blood cells (including leukoyctes) in patients receiving high-dose cancer therapy with marrow transplantation. A review of randomised trials involving patients receiving autologous bone marrow transplantation revealed significantly shorter durations to re-engraftment (ANC >1000/µl), number of antibiotic treatment days and time to hospital discharge following administration of rhGM-CSF. Whether the decreased incidence of febrile neutropenic or reduced numbers of antibiotic treatment days is the result of earlier granulocyte recovery or more functionally efficient neutrophils is currently unkown. Nevertheless, rhGM-CSF appears to be a useful adjunct to BM transplantation.

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Synergistic Interactions in Haemopoiesis: Biological Implications and Clinical Use

T. M. Dexter

Growth factors promote the survival and proliferation of haemopoietic stem and progenitor cells, and in their absence the haemopoietic cells undergo apoptosis and die. The results of studies reported here indicate that multipotent stem cells have receptors for most, if not all, of the growth factors, but that even saturated binding of the receptors for a single growth factor is not sufficient to transduce an effective stimulus for the proliferation of these cells (possibly due to very low receptor numbers). However, when the growth factors are combined synergistic effects can be seen. Studies in which stem cell factor was used in combination with other growth factors showed that stem cell factor allowed the survival of stem cells, while a second growth factor (granulocyte-macrophage colony-stimulating factor) stimulated the stem cells to develop normally. Stem cell factor was also shown to alter the dose-response relationships of developing haemopoietic cells for other growth factors.
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THE REGULATION OF NORMAL HAEMOPOIETIC CELL DEVELOPMENT IN THE BONE MARROW

ALL MATURE blood cells are derived from a small number of stem cells which, in adults, are resident in the bone marrow [1]. These stem cells undergo proliferation, differentiation and development and with increasing maturation the cells are released into the circulation. Stem cells possess the potential for extensive self-renewal and they can also differentiate to produce progeny that become progressively more restricted in their developmental options and that possess little or no ability to undergo self-renewal. Ultimately, at least nine different types of mature cells are produced: neutrophils, basophils, eosinophils,

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