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HEMATOLOGICAL RECOVERY AFTER AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR HIGH-GRADE NON HODGKIN'S LYMPHOMAS: A SINGLE CENTER EXPERIENCE

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ABSTRACT

Background. **Both rhGM-CSF and rhG-CSF can accelerate hematological recovery after high-dose therapy and autologous bone marrow transplantation in patients with high grade non Hodgkin's lymphoma and reduce transplant-related morbidity after ABMT.**

Methods. **The clinical course of 23 non randomized patients was analyzed and compared with a historical control group of 10 patients. Ten patients received GM-CSF at a dose of 10 μg/kg in a 6-h IV infusion, and 13 received G-CSF at a dose of 5 μg/kg subcutaneously. Control patients received no GFs.**

Results. **Mean granulocytic recovery to 0.5×10^9/L was obtained 13.1±3.2 days after marrow reinfusion in the G-CSF arm vs 16±2.7 in GM-CSF pts ($p = 0.03$) and vs 19.6±7.6 in controls ($p < 0.01$); this reduction led to a statistically significant shorter duration of fever and parenteral antibiotic therapy. Platelet recovery to 20×10^9/L was not significantly influenced by GFs.**

Conclusions. **These results indicate that only G-CSF accelerates hematological recovery after high-dose chemotherapy and autologous bone marrow transplantation and induces a significant decrease in terms of infection morbidity and duration of hospital stay.**

Key words: high-grade non Hodgkin's lymphoma, autologous bone marrow transplantation, growth factors

Intensive chemotherapy (CHT) followed by autologous bone marrow transplantation (ABMT) finds progressively widespread utilization in the treatment of several hematological malignancies and solid tumors.[1,2] Unfortunately, ABMT is still associated with a relatively high rate of morbidity and mortality because of severe myelosuppression.[3] In fact, the most frequent causes of transplant-related death are infections, followed by the hemorrhagic syndrome and major organ toxicity.[4,5] The incidence of severe infections is strictly related to the duration of neutropenia. Recombinant human growth factors (GFs) are a family of glycoproteic hormones that regulate blood cell production and differentiation.[6] In particular, granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) are now commonly used to accelerate neutrophil recovery after myeloablative chemotherapy[7] and ABMT.[8-12] Here we report our experience with 23 non-randomized patients (pts) with high grade non Hodgkin's lymphoma (NHL) submitted to ABMT and treated with GFs immediately after marrow reinfusion. Their hematological recovery was compared with a historical control group of 10 matched pts who did not

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receive any GFs. The impact of GFs upon transplant-related morbidity, in terms of infectious episodes and documented sepsis, was assessed with particular attention being paid to possible differences in effects between GM-CSF and G-CSF.

Patients and methods

Patients

Twenty-three patients with histologically proven NHL according to the Kiel classification[13] were submitted to autologous bone marrow transplantation between December, 1989 and February, 1993. All of them had a Karnowsky index (KI) of at least 70%, without major organ involvement. Ten patients were treated with GM-CSF, 13 with G-CSF. They were compared in terms of hematological recovery and transplant-related morbidity with a control group of NHL pts treated from September, 1982 to September, 1990 with identical high-dose chemotherapy and ABMT, but without GFs; this latter group was matched with our study pts for histology, age, KI, chemotherapy before harvest, and status of the disease at transplant. The characteristics of the 23 study pts and 10 controls are shown in Table 1.

No histopathological evidence of marrow involvement was found, either in the study patients or in the control group. Complete blood cell count, platelet count, differential, biochemical profile, coagulation test and urinalysis were performed pre ABMT. Chest radiography, electrocardiogram, bacterial and fungal cultures and viral serology were also carried out; tumor extent was accurately evaluated before treatment.

Bone marrow collection, chemotherapy and supportive care

Bone marrow was harvested from bilateral posterior iliac crests under general anesthesia. At least 1×10^8 mononucleated cells per kg body

Table 1. Patient characteristics.

	GM-CSF	*G-CSF*	*No GFs*
N° patients	10	13	10
Male	4	7	5
Median age (range)	19.5 (15-35)	28 (18-53)	24.5 (15-45)
Histology:			
ALC	8	6	3
T-LB	–	3	1
CB	–	1	5
Burkitt	–	1	–
IB	–	1	1
Other	2	1	–
Disease status at ABMT			
CR	1	2	4
PR	3	5	1
untreated relapse	–	1	–
resistant relapse	3	1	3
responding relapse	1	2	2
primary Refractory	1	2	–
diagnosis	1	–	–
Previous treatment			
no therapy	1	–	–
1 line	5	7	6
2 lines	3	3	2
> 2 lines	1	3	2

ALC: anaplastic large cell lymphoma; T-LB: T-lymphoblastic lymphoma; CB: centroblastic lymphoma; IB: immunoblastic lymphoma.

Table 2. Conditioning regimen: BAVC.

Drug	*Dose*	*Days*
BCNU	200 mg/sm	–4
cytarabine	150 mg/sm every 12h	–5 to –2
etoposide	150 mg/sm every 12h	–5 to –2
cyclophosphamide	45 mg/kg daily	–5 to –2
ABMT		0

weight were required for ABMT. All patients were submitted to only one harvest (in the study and control groups); marrow buffy-coat was cryopreserved at –1°C/minute in 10% dimethylsulfoxide (DMSO) and 20-30% autologous plasma, and stored at –196 °C.

All the patients received the same BAVC conditioning regimen[14-16] consisting of: BCNU 200 mg/sm intravenously (IV) on day –4; cytarabine 150 mg/sm IV every 12h on days –5, –4, –3, –2; etoposide (VP-16) 150 mg/sm IV every 12h on days –5, –4, –3, –2; cyclophosphamide 45 mg/kg body weight IV per day on days –5, –4, –3, –2 (Table 2). Bone marrow was infused on day 0. Patients were treated in a private room without laminar air flow and placed on a diet low in bacterial and fungal content (not sterile food).

According to the policies of our Institute for the period from 1982 to 1993 with regard to oral antimicrobic prophylaxis, patients transplanted before 1987 received trimethoprim sulphate; those transplanted in 1987-88 received neomycin and colistin, while patients transplanted after 1988 received a quinolone prepa-

Table 3. Number of reinfused cells.

	GM-CSF	*G-CSF*	*no GFs*
N. evaluable patients	10	12	10
Mononucleated cells infused x 10^8/kg*	1.7 (1.3-2.2)	1.6 (0.7-3.1)	1.7 (1.1-3.6)
CFU-GM infused x 10^4/kg*	5.3 (0-17.7)	2.0 (0-8.8)	3.2 (0.8-21.8)

*median (range)

ration. A complete blood cell count and biochemical profile were done daily until recovery. Hemoglobin was maintained over 8 g/dL by transfusion of packed red cells, and the platelet count was maintained above 10×10^9/L by single donor apheresis or random donor platelet transfusions. All blood products were irradiated with ^{60}Co 2000 cGy. Parenteral antibiotics were given by protocol and started after the onset of fever (> 38°C)[17] during neutropenia, and stopped when neutrophil count was $>0.5\times10^9$/L without any evidence of clinical infection. First-line intravenous antibiotic therapy included the association of a β-lactam and an aminoglycoside until 1987, and of an aminoglycoside, a third generation cephalosporin and a glycopeptide thereafter. Patients were discharged when they no longer required parenteral antibiotics or nutritional therapy and other acute medical problems had resolved. GF administration was continued on an outpatient basis if required.

Growth factor administration

RhGM-CSF (Sandoz/Schering) was administered in a 6-h IV infusion at a dose of 10 μg/kg/day from day 0 and stopped when the neutrophil count exceeded 0.5×10^9/L for 3 consecutive days. RhG-CSF (Dompè Biotec/Roche) was administered daily as a single subcutaneous injection at a dose of 5 μg/kg/day from day +1. G-CSF, like GM-CSF, was stopped when neutrophil count exceeded > 0.5×10^9/L for 3 consecutive days.

Statistical analysis

All patient characteristics are expressed as median (range). Values for hematological recovery and clinical aspects are expressed as means ± standard deviation (SD). All data in the three arms were compared using the Wilcoxon rank-sum. P-values were always two-sided and were considered significant when < 0.05.

Results

One patient who received G-CSF died on day +9 from myocardial infarction, and his data were not evaluable for this study. For the

remaining 22, the median number of infused mononuclear cells and CFU-GM are shown in Table 3. There are no significant differences among the 3 groups. All patients showed complete engraftment. No one interrupted GFs or needed dose reduction because of drug-related toxicity; only 3 pts treated with GM-CSF displayed moderate side effects, consisting of bone pain and myalgias (grade I or II). G-CSF was well tolerated without any side effect.

Myeloid recovery in the three groups of pts is shown in Table 4. Time to reach $\geq 0.2\times10^9$/L neutrophils was significantly shorter for pts receiving G-CSF (11.4 days) compared with that for pts treated with GM-CSF (13.7 days) ($p = 0.04$). The mean time to achieve 0.5×10^9/L neutrophils was also significantly reduced in G-CSF pts (13.1 days) with respect to GM-CSF (16 days) and controls (19.6 days) ($p = 0.03$ and $p < 0.01$, respectively). There was no statistically significant effect of GFs on red cell or platelet recovery, although GM-CSF-treated pts required the shortest time to achieve 20×10^9/L and 50×10^9/L platelets. GM-CSF pts received 7.9 mean units of packed red cells, G-CSF 6, compared with 6.4 in the controls.

The mean number of platelet transfusions (1 unit of platelets corresponds to 1 unit from single donor apheresis or 6 units of random-donor platelets) was 4.8, 6.7 and 5.6 in GM-CSF, G-CSF and control pts, respectively. Severe neutropenia with a high risk of infectious complications occurred in all pts.

The mean duration of neutrophil count below 0.1×10^9/L showed a difference in favor of G-CSF pts vs GM-CSF (p = ns) and vs controls ($p = 0.01$). One patient in the G-CSF group and 1 of the controls did not develop fever during this phase.

The mean number of days with fever > 38° C was shorter in G-CSF pts (3.2) compared with GM-CSF (6.7) ($p = 0.03$) and controls (6.4) (p = ns); the days of parenteral antibiotic therapy were 14, 7.9 and 15.9 in the GM-CSF, G-CSF and control arms, respectively ($p = 0.04$ G-CSF vs GM-CSF; $p = 0.04$ G-CSF vs controls). Positive blood cultures were detected in 50%, 58% and 40% of febrile episodes in the GM-CSF, G-CSF and control groups. There was a trend toward a shorter duration of hospital stay for GF pts; statistical significance was shown for G-CSF pts vs controls ($p < 0.01$) and for G-CSF vs GM-CSF pts ($p = 0.04$).

Tumor response and follow-up of all 33 subjects are shown in Table 5. As of June, 1993, 16 of them are still living after a follow-up of 3 to 128 months: 15 out of 16 are in continuous CR and 1 patient is alive with lymphoma at 20 months from ABMT. There was only 1 transplant-related death (myocardial infarction, day +9 from ABMT). Fifteen patients died after ABMT from relapse and/or disease progression.

Table 4. Hematological and clinical response.

	GM-CSF	*p**	*G-CSF*	*p**	*No GFs*
No. of patients	10		12		10
Days to 0.2×10^9/L ANC	13.7 (± 2.4)	0.04	11.4 (± 2.4)	ns	13.4 (± 3.5)
Days to 0.5×10^9/L ANC	16.0 (± 2.7)	0.03	13.1 (± 3.2)	< 0.01	19.6 (± 7.6)
Days to 20×10^9/L PLT	16.8 (± 2.8)	ns	21.1 (± 11.9)	ns	19.6 (± 6.8)
Days to 50×10^9/L PLT	18.9 (± 3.6)	ns	25.4 (± 16.8)	ns	23.5 (± 9.7)
Days with $< 0.1 \times 10^9$/L ANC	9.6 (± 3.5)	ns	7.2 (± 2.4)	0.01	10.1 (± 2.4)
Days of fever > 38°C	6.7 (± 4.0)	0.03	3.2 (± 2.1)	ns	6.4 (± 6.4)
Days on parenteral antibiotics	14.0 (± 7.2)	0.04	7.9 (± 5.1)	0.04	15.9 (± 11.8)
Days of hospitalization (post ABMT)	21.6 (± 5.2)	0.04	18.1 (± 5.1)	< 0.01	31.3 (± 11.8)

ANC: Absolute neutrophil count. *: p-value between GM-CSF and G-CSF patients; **: p-value between G-CSF patients and controls. No statistical significance was observed between the GM-CSF and controls.

Table 5. Patient characteristics and disease outcome.

Patient	*Age/sex*	*Status at ABMT*	*ABMT date yy/mm/dd*	*Response*	*PFS months*	*Survival months*	*Present status*
GM-CSF							
SF	17/F	Res Rel	89/12/12	PR	3	7	Dead Ly
MM	26/F	PR	90/03/08	CR	39	39+	Alive CR
CP	31/F	Resp Rel	90/06/27	CR	36	36+	Alive CR
DC	17/M	Res Rel	90/07/23	CR	35	35+	Alive CR
MG	22/M	PR	91/01/16	CR	29	29+	Alive CR
MB	17/F	Refractory	91/02/13	PR	7	10	Dead Ly
TM	15/F	Diagnosis	91/04/03	CR	5	17	Dead Ly
MA	16/M	PR	91/05/03	CR	25	25+	Alive CR
PA	26/M	CR	91/05/31	CR	24	24+	Alive CR
LM	35/F	Res Rel	91/06/03	CR	3	5	Dead Ly
G-CSF							
MG	45/M	PR	91/08/19	CR	22	22+	Alive CR
FM	32/M	PR	91/10/21	PR	3	20+	Alive Ly
MS	28/M	Resp Rel	91/10/28	CR	3	8	Dead Ly
BA	18/F	Res Rel	91/11/18	CR	3	7	Dead Ly
CV	30/F	Refractory	91/12/27	Failure	–	6	Dead Ly
RA	20/F	PR	92/01/22	CR	9	17	Dead Ly
SM	35/M	Resp Rel	92/01/25	CR	3	6	Dead Ly
SA	53/F	PR	92/02/17	CR	16	16+	Alive CR
AS	24/M	PR	92/04/01	CR	14	14+	Alive CR
MM	25/F	Refractory	92/06/08	Failure	–	4	Dead Ly
AL	26/F	CR	92/09/11	CR	9	9+	Alive CR
ME	33/M	Resp Rel	92/10/09	NE	–	0.5	Dead TRT
GF	19/M	CR	93/03/03	CR	3	3+	Alive CR
No growth factors							
CM	28/F	Resp Rel	82/09/20	Failure	–	3	Dead Ly
CA	45/M	Resp Rel	82/10/11	CR	128	128+	Alive CR
CP	45/M	Res Rel	83/06/27	CR	3	8	Dead Ly
PC	29/F	PR	84/11/14	PR	103	103+	Alive CR
PA	30/F	Res Rel	86/04/08	Failure	–	6	Dead Ly
SS	21/F	CR	87/10/20	CR	7	13	Dead Ly
CG	17/M	CR	90/06/01	CR	36	36+	Alive CR
SC	19/M	Res Rel	90/08/28	Failure	–	12	Dead Ly
VS	19/F	CR	90/10/24	CR	32	32+	Alive CR
PN	15/M	CR	91/03/18	CR	27	27+	Alive CR

PFS= Progression Free Survival; Resp Rel= Responding Relapse; Res Rel= Resistant Relapse; PR= Partial Remission; CR= Complete Remission; NE= Not Evaluable; TRT= Transplant-Related Toxicity; Ly= Lymphoma.

No difference in overall or progression-free survival was observed among the 3 groups of patients.

Discussion

Several randomized and non-randomized studies in recent years have demonstrated that administration of rhGFs (GM-CSF[18-26] and G-CSF[26-30]) significantly shortens the duration of neutropenia after intensive chemotherapy followed by autologous bone marrow reinfusion performed for hematological malignancies and solid tumors. Moreover, the acceleration of neutrophil recovery induced by rh-GFs has been shown to decrease transplant-related morbidity, with a parallel reduction in the overall cost of the entire therapeutic procedure.[31] However, it has not yet been accertained which of the two growth factors is more active in this clinical setting and more cost-effective.

We investigated the effects of GM-CSF and G-CSF on hemopoietic reconstitution in 23 consecutive patients with high grade non-Hodgkin's lymphoma receiving high-dose chemotherapy and ABMT, and compared them with a historical group of NHL patients who received identical intensive CHT and ABMT only. The whole population studied was homogeneous in terms of histological diagnostic criteria and conditioning regimen (BAVC: BCNU, Ara-C, VP-16, cyclophosphamide), and was comparable with regard to age, sex, KI, disease status at transplant, number of lines of pre-transplant therapy, number of mononucleated cells and CFU-GM reinfused, nursing and supportive care, barrier isolation. The only differences in clinical management concerned oral antibiotic prophylaxis and parenteral antinfection therapy, due to the changing policies in our Institution over the 10-year period during which this cohort of patients was treated. Another difference was the route of GF administration: GM-CSF was infused intravenously over 6 hours, while G-CSF was given as a single subcutaneous injection. However, the biological effects of GM-CSF on mature blood cells and on granulo-monocyte and erythroid progenitors are irrespective of the route of administration,[32, 33] and at present subcutaneous delivery is preferred because it is more convenient.

The incidence and seriousness of fever and infectious complications after ABMT are directly related to the length of most severe neutropenia; the time in which absolute neutrophil count (ANC) is less than 0.1×10^9/L is the period at highest risk.

Our data, even though they come from a non randomized study on a limited number of pts, show that G-CSF-treated subjects have faster granulocyte recovery after ABMT compared with fully matched GM-CSF-treated pts and historical controls who did not receive any growth factors (7.2 days with $< 0.1\times10^9$/L ANC vs 9.5 days for GM-CSF-treated patients vs 10.1 days for no-growth-factor patients). Although the crude incidence of documented septic episodes did not differ among the three groups, their severity was substantially reduced in the G-CSF arm due to the concurrent reduction of agranulocytosis. In fact, G-CSF-treated patients had the lowest number of febrile days (3.2 vs 6.7 vs 6.4, respectively), received less parenteral antibiotics (7.9 days vs 14 vs 15.9) and were discharged earlier from the hospital (18.1 days vs 21.6 vs 31.3).

Both GM- and G-CSF were very well tolerated: no patient had to discontinue treatment or reduce the dosage. Moderate bone pain and myalgias were observed in 3 pts treated with GM-CSF, while G-CSF administration was absolutely devoid of any side effect, confirming all the findings of other studies about the complete safety of this molecule.[27-30]

In a previous study[34] we suggested that the single most important factor influencing the rate of hematological reconstitution after ABMT for NHL was chemotherapy before marrow collection. Indeed pts who were harvested and transplanted at diagnosis had a significantly faster recovery for both neutrophils and platelets. Untreated pts conditioned by BAVC chemotherapy reached 0.5×10^9/L ANC on day 14.8 ± 1.9 and 50×10^9/L plt on day 15.9 ± 3.4. Almost identical results were achieved in the present study using G-CSF, thus showing that growth factor activity allows by-passing of the pre-harvesting chemotherapy-induced damage

to the stem cell compartment and marrow micro-environment.

GFs are currently being utilized more and more to accelerate hemopoietic recovery after high-dose chemotherapy and autologous marrow rescue because the reduction of treatment-related morbidity linked to the shortening of neutropenia makes them cost-effective. Our findings suggest that G-CSF may offer an advantage over GM-CSF with regard to time to granulocyte recovery, number of febrile episodes, days on parenteral antibiotics and length of hospitalization. This favorable activity is coupled with a lack of side effects. Moreover, exciting prospects have been suggested by the possible combination of these GFs with early-acting cytokines, such as stem cell factor or interleukin-3[35-36] which could potentially lead to a minimization of the period of cytopenia after ABMT.

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