



Adverse side-effects associated with G-CSF in patients with chronic myeloid leukemia undergoing allogeneic peripheral blood stem cell transplantation

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Summary:

Administration of the myeloid growth factor G-CSF after allogeneic hematopoietic stem cell transplantation is usually well tolerated, and associated with rapid hematopoietic engraftment. We report a high incidence (50%) of side-effects associated with post-transplant G-CSF in patients with chronic phase chronic myeloid leukemia undergoing allogeneic HLA-identical sibling peripheral blood stem cell transplantation. One or more of the following signs and symptoms were observed shortly after the subcutaneous injection of G-CSF: dyspnea, chest pain, nausea, hypoxemia, diaphoresis, anaphylaxis, syncope and flushing. These reactions led to discontinuation of G-CSF in the majority of patients. Predictive factors could not be identified, and the underlying mechanism leading to these reactions is unknown. Bone Marrow Transplantation (2000) 25, 1197–1201.

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chronic myeloid leukemia in chronic phase (CP-CML), but not in patients with other diagnoses, undergoing allogeneic HLA-identical sibling donor PBSC transplantation. Characteristics of these adverse reactions are herein described. In an attempt to identify factors that might predict these reactions, this group was compared to CP-CML patients who tolerated the administration of G-CSF uneventfully.

Materials and methods

Patients

Records of CP-CML patients who underwent allogeneic matched sibling donor PBSC transplantation or mobilization with G-CSF for autologous stem cell storage were reviewed, and specifically designed case report forms were completed. For purposes of this analysis, CP-CML patients were divided into three groups: allogeneic PBSC transplant recipients who did (group 1) or did not (group 2) experience a reaction to G-CSF, and patients who were mobilized with G-CSF for autologous stem cell storage (group 3). Administration of G-CSF for autologous stem cell mobilization was tolerated uneventfully in all CP-CML patients. Before transplantation or stem cell mobilization, none of the CP-CML patients was previously exposed to G-CSF.

Allogeneic PBSC transplants

Conditioning included cyclophosphamide (60 mg/kg/day i.v. on days –2 and –1), methylprednisolone (1000 mg/day i.v. on days –2 and –1), and low dose (550 cGy) total body irradiation delivered as a single dose at a high-dose rate (30 cGy/min) on day 0.¹⁶ Oral cyclosporin A (12.5 mg/kg/day) was initiated on day –2 as a single agent for GVHD prophylaxis. G-CSF (Neupogen; Amgen, Thousand Oaks, CA, USA), 10 µg/kg/day subcutaneously (s.c.), was started on post-transplant day 1, and discontinued upon neutrophil engraftment. Donors were mobilized with either G-CSF at 10 µg/kg s.c. daily for 5 days ($n = 13$), GM-CSF at 10 µg/kg s.c. daily for 5 days ($n = 1$), or with a combination of G-CSF and GM-CSF ($n = 6$). PBSC were collected by a single large volume apheresis (20 l). Except for red cell depletion for ABO incompatibility ($n = 4$), the pheresis product was unmanipulated and administered immediately to the recipient.

Peripheral blood stem cells (PBSC) are gradually becoming the major source of hematopoietic progenitor cell support for patients undergoing allogeneic transplantation. Enthusiasm for transplantation using cytokine-mobilized PBSC has increased in the past few years after encouraging results of initial phase II studies demonstrated faster hematopoietic engraftment,^{1,2} shorter hospitalization and improved early immune reconstitution.³ Accelerated neutrophil recovery is associated with post-transplant administration of myeloid hematopoietic growth factors in recipients of matched sibling bone marrow transplantation.^{4–8} G-CSF is usually well tolerated^{7–11} and medullary bone pain is the most frequently reported side-effect.¹² Other less common adverse effects include headaches, generalized musculoskeletal pain, and exacerbation of underlying inflammatory skin disease.¹³ Two reports have described an anaphylactic-like reaction associated with administration of G-CSF.^{14,15}

In this report, a high incidence of side-effects associated with post-transplant G-CSF was observed in patients with

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Mobilization and collection of autologous PBSC

CP-CML patients were mobilized with G-CSF at 10 $\mu\text{g/kg}$ s.c. daily for 5 days. PBSC were collected by a large volume apheresis (20 l) and the pheresis product was stored in liquid nitrogen at -190°C .

Adverse reactions to G-CSF

An adverse reaction to G-CSF was defined as an unexpected clinical manifestation that occurred shortly after administration of G-CSF, and could not be attributed to a transplant-related complication or any other medication. Full description of the reaction was obtained from detailed physicians and nurses' notes.

Statistical analysis

Statistical analyses were performed using SAS v.8 (SAS Institute, Cary, NC, USA). The three study groups were compared with respect to age at the time of transplantation, gender, splenic enlargement at the time of diagnosis, prior treatment with interferon alfa ($\text{IFN}\alpha$), presence of pre-existing cardio-pulmonary disease, pre-transplant corrected alveolar diffusion capacity (DLCOc), type or combination of growth factor used to mobilize donors, red cell depletion of the stem cells, number of CD34^{+} cells transplanted, doses of G-CSF, white blood count (WBC) and differential pre-G-CSF, and 1, 2 and 3 days after initiation of G-CSF. All comparisons were performed using Fisher's exact test, or a Kruskal-Wallis's rank sum test, where appropriate. In addition, pair-wise comparisons of group 1 with each of groups 2 and 3 were carried out when indicated. Because of the small number of patients in this study, only univariate models were examined.

Results

Reactions to G-CSF

Between November 1995 and August 1999, 78 patients with hematologic malignancies, including 20 with CP-CML, were conditioned with cyclophosphamide, methylprednisolone and single-dose TBI for allogeneic HLA-identical sibling donor PBSC transplantation followed by post-transplant G-CSF. An unexpected, yet clinically dramatic, adverse reaction occurred, a median of 60 min (range, 30–300) from the first ($n = 7$) or second ($n = 3$) s.c. injection of G-CSF, in 10 of the 20 patients with CP-CML (50%). Adverse reactions to G-CSF were not observed in patients with diagnoses other than CP-CML. Characteristics of these reactions included one or more of the following signs and symptoms: dyspnea (8), chest pain (3), nausea (5), hypoxemia (pulse oximeter measurement of less than 90%) requiring oxygen supplements (2), diaphoresis (6), hypotension in the setting of an anaphylactic reaction (2), loss of consciousness from syncope (3) and flushing (3). Hydrocortisone and antihistamine were administered to all patients resulting in rapid resolution of symptoms. G-CSF was discontinued in all patients after adverse

reactions occurred. Four patients were rechallenged with G-CSF after premedication with hydrocortisone and antihistamine, and symptoms did not recur in two. Therefore, G-CSF was resumed uneventfully until neutrophil engraftment in those two patients only.

After recognition of the association between the diagnosis of CP-CML and the occurrence of adverse reactions to G-CSF, the schedule of G-CSF post allogeneic sibling donor PBSC transplantation was altered to start day +5. With this modified G-CSF schedule, eight subsequent consecutive patients with CP-CML received and tolerated post-transplant G-CSF uneventfully.

Predictive factors

In an attempt to determine predictive factors for these unexpected reactions to G-CSF, this cohort of patients who experienced adverse reactions to G-CSF (group 1) was compared to CP-CML patients who tolerated uneventfully the administration of G-CSF either post allogeneic PBSC transplantation (group 2, $n = 10$) or for mobilization of autologous stem cells (group 3, $n = 14$). Table 1 summarizes patient characteristics and variables analyzed for the three patient groups. Patients in all three groups were comparable with regard to age, gender, pre-existing cardio-pulmonary condition and the presence of splenomegaly at the time of diagnosis of CML. All patients in group 2, and 12 of 14 patients in group 3 received $\text{IFN}\alpha$ as part of their pre-transplant management of CML, while only five of 11 patients in group 1 had a trial of $\text{IFN}\alpha$ pre-transplant. This difference was not statistically significant ($P = 0.1$). The type or combination of growth factor used to mobilize donors, the number of stem cell products depleted of red cells, and the number of stem cells infused were comparable between the two transplant groups. One day prior to starting G-CSF, median WBC counts were 13.5, 11.6, and 12.3 in groups 1, 2 and 3, respectively ($P = 0.48$). The WBC differential was also comparable among the three groups. In particular, no increases in the absolute numbers of basophils or monocytes were observed (Table 2).

The doses of G-CSF administered were comparable among the three patient groups. When assessed 1, 2 and 3 days after initiation of G-CSF, patients in group 3 had the highest WBC count. When compared to group 2, group 1 patients had higher WBC counts 1 and 2 days after initiation of G-CSF; however, this difference was not statistically significant (41.6 vs 33, $P = 0.42$, and 35.9 vs 27.6, $P = 0.6$, respectively). After initiation of G-CSF, a marked left shift was observed in all three groups with neutrophils and bands representing the vast majority of the WBC (Table 2).

Outcomes

Post-transplant G-CSF was discontinued in all but two patients in group 1. However, when compared to patients in group 2, time to neutrophil engraftment for those patients who did not receive G-CSF was not clinically different (12.8 vs 11.4 days, $P = 0.05$). The incidence of acute GVHD IBMTR severity indices A-B, and C-D were 70 vs 90%, and 20 vs 0% ($P = 0.4$), for groups 1 and 2, respect-

Table 1 Patient characteristics and factors analyzed in the three patient groups (*n* = 34)

	Group 1 (<i>n</i> = 10)	Group 2 (<i>n</i> = 10)	Group 3 (<i>n</i> = 14)	<i>P</i> value
Median age in years (range)	48 (21–60)	43 (23–61)	45 (21–57)	0.73
Sex (M/F)	5/5	5/5	6/8	1.0
Prior treatment with IFN α	5/10	9/10	12/14	0.11
Splenomegaly at diagnosis	6/10	6/10	7/14	0.83
Pre-existing cardio-pulmonary condition	3/10	3/10	7/14	0.49
Median DLCOc (range)	72 (56–100)	86 (74–100)	88.5 (62–96)	0.36
G-CSF + GM-CSF for donor mobilization	4/10	3/10	N/A	0.63
Red cell depletion of PBSC	5/10	4/10	N/A	1.0
Median CD34 ⁺ cells transplanted (range)	6.0 $\times$ 10 ⁶ (3.1–46.5)	6.2 $\times$ 10 ⁶ (2.8–16.2)	N/A	0.54
Median G-CSF dose in μ g (range)	780 (560–925)	776 (620–1000)	915 (425–1150)	0.45
Median WBC/ μ l pre-GCSF (range)	13.5 (2–39)	11.6 (4.4–55)	12.3 (6–46)	0.48
Median WBC/ μ l day 1 G-CSF (range)	40.9 (9.7–70)	30.5 (3.2–89)	55.9 (27–90)	0.09
Median WBC/ μ l day 2 G-CSF (range)	31.4 (6.8–71)	24 (8.3–86)	85 (30.4–177)	0.02 ^a
Median WBC/ μ l day 3 G-CSF (range)	11.3 (1–24)	7 (3–33)	56.3 (40–115)	0.0002 ^a

^aPair-wise comparison of group 3 with each of groups 1 and 2.**Table 2** WBC counts and differential (mean (s.d.)) before and after initiation of G-CSF in the three patient groups

	Pre-G-CSF	Day 1 G-CSF	Day 2 G-CSF	Day 3 G-CSF
Group 1				
WBC (/ μ l)	14.7 (10.7)	41.6 (21.5)	35.9 (23.5)	12.2 (8.8)
% Neutrophils	87 (13)	90 (6)	94 (4)	92 (12)
% Bands	9 (12)	9 (6)	4 (5)	3 (4)
Group 2				
WBC (/ μ l)	13.8 (15.4)	33.0 (24.4)	27.6 (23.9)	9.0 (9.1)
% Neutrophils	84 (4)	83 (3)	90 (2)	90 (4)
% Bands	6 (2)	14 (3)	6 (2)	3 (1)
Group 3				
WBC (/ μ l)	17.3 (13.5)	53.9 (19.9)	84.9 (51.9)	67.7 (27.3)
% Neutrophils	62 (3)	73 (6)	80 (4)	67 (5)
% Bands	5 (2)	11 (3)	6 (3)	15 (4)

ively. With a median follow-up of 12 months (range, 2–30), transient cytogenetic relapse was observed in two patients (both in group 2), and one patient (group 2) died from progressive acute GVHD after withdrawal of immunosuppression for hematologic relapse.

Discussion

This is the first report describing a high incidence of adverse side-effects following post-transplant administration of G-CSF. Reactions were observed shortly after the subcutaneous injection of G-CSF, and led to its discontinuation in almost all patients. The underlying mechanism is unknown, and predictive factors could not be identified by the present analysis. It is of interest that these reactions were observed exclusively in patients with CP-CML, and no reactions to post transplant G-CSF were observed in 58 patients with diagnoses other than CP-CML.¹⁷ It is unclear if these reactions are CML disease-specific or due to the elevated white blood cell counts at the time G-CSF was

initiated. In juvenile CML, both GM and erythroid progenitor cell lines display marked (10-fold) and selective hypersensitivity, as assessed by hematopoietic growth factor dose–response curves, to the addition of GM-CSF, but not to G-CSF.¹⁸ Reactivity of CML cell lines in response to myeloid growth factor stimulation has not been described.

With a short preparative regimen (2 days) that includes high-dose methylprednisolone, a relatively high WBC was observed upon initiation of G-CSF 1 day post transplant in patients with CP-CML (Table 1). This observation is not surprising as CP-CML patients were not cyto-reduced prior to transplantation, and corticosteroids increase the total blood neutrophil pool by increasing efflux from the marrow. Timing of initiation of G-CSF in relation to the WBC count post transplant may be an important factor for the development of these reactions, and may provide a possible explanation as to why such adverse side-effects have not been previously described. Indeed, in most transplant centers performing allogeneic PBSC transplants, post-transplant G-CSF is either omitted,^{19–22} or started on day +7 (following the last dose of prophylactic methotrexate) at a

time when patients have become aplastic.²³ After recognition of these reactions in CP-CML patients undergoing allogeneic sibling donor PBSC transplant at our institution, delaying the initiation of G-CSF to post transplant day +5 prevented the occurrence of these adverse side-effects.

Elevated WBC alone at the time G-CSF was started may not account for the development of these adverse reactions. Indeed, CP-CML patients receiving G-CSF for stem cell mobilization tolerate G-CSF remarkably well,^{24,25} despite very high circulating WBC counts (Table 1). This observation suggests that in order for these reactions to occur, the addition of G-CSF in the presence of a high circulating WBC count may require prior activation. During the preparative regimen, multiple cytokines are released as part of what has been described as a 'cytokine storm',^{26,27} resulting in activation of various host cells. It is possible that addition of G-CSF could have induced additional cytokine release leading to the observed clinical manifestations. Alternatively, these reactions may be due to the addition of pharmacologic doses of G-CSF in the setting of high endogenous G-CSF levels. However, a reverse correlation between blood neutrophil counts and serum G-CSF levels exists and is demonstrated by lower serum levels of G-CSF in patients with CP-CML as compared to healthy individuals.²³ After allogeneic bone marrow transplantation, low serum levels of G-CSF are observed in CP-CML patients before infusion of the allogeneic marrow. Endogenous G-CSF levels subsequently increase 1 day post transplant, and peak on day +10 before starting to decline.^{28,29} While all patients start with low G-CSF levels, only patients with a subsequent late engraftment present higher serum G-CSF levels on day +1.³⁰ Serum G-CSF or cytokine levels were not obtained in our patients. However, the prompt neutrophil engraftment observed among patients who did not tolerate G-CSF suggests that endogenous G-CSF levels may not have been elevated.

Adverse clinical manifestations associated with post-transplant G-CSF resolved rapidly with administration of anti-histamine and corticosteroids, suggesting a possible role for a histamine-mediated reaction. Limited data are available on the effects of G-CSF on basophils and mast cells. In one study, survival of cultured basophils obtained from healthy individuals was not affected by the addition of G-CSF, while IL-3 and to a lesser extent GM-CSF maintained the number of viable cells.³¹ G-CSF administered to allergic patients was associated with increases in number of circulating basophils, reduction in the histamine content per basophil and reduction of histamine release by basophils.³² In patients with CP-CML, differentiation of neoplastic basophil/mast cell precursors was observed with addition of G-CSF.³³ However, histamine release and histamine levels were not reported.

Most patients complained of dyspnea. Rapid pulmonary sequestration of blood neutrophils associated with dyspnea and peripheral blood neutropenia was described 5–60 min after intravenous bolus doses of GM-CSF, and less commonly after G-CSF.³⁴ In our patients, hourly blood counts were not obtained, as these reactions were not recognized initially. Underlying cardio-pulmonary disease or lower pre-transplant corrected alveolar diffusion capacity (DLCOc) was not a predisposing factor.

In summary, we conclude that administration of G-CSF post allogeneic sibling donor PBSC transplantation for patients with CP-CML was frequently associated with significant adverse side-effects. These reactions could not be predicted, and led to discontinuation of G-CSF in the vast majority of patients. Delaying the initiation of G-CSF post transplant may prevent such reactions in CP-CML.

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