

CLINICAL STUDY

The use of granulocyte colony stimulating factor after autologous hematopoietic stem cell transplantation

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ABSTRACT

OBJECTIVE: Restrospective study to evaluate the efficacy of early vs. delayed initiation of G-CSF after autologous hematopoietic stem cell transplantation (AH SCT) in patients with lymphoid malignancies.

BACKGROUND: Granulocyte colony stimulating factor (G-CSF) is commonly used after AH SCT to accelerate stem cell engraftment to minimize the morbidity and mortality associated with prolonged neutropenia. However, there is no consensus on the optimal timing of G-CSF after HSCT.

METHODS: A total of 117 patients with lymphoid malignancies who underwent AH SCT were included. All patients received G-CSF (filgrastim 5 µg/kg s.c.) daily after AH SCT (43 patients on day 6–8 and 74 patients on day 3 or 4). All patients received standard conditioning regimen for the underlying disease, and standard supportive treatment, including treatment of febrile neutropenia.

RESULTS: The incidence of severe neutropenia was 81 % vs 17 %, and very severe neutropenia 61 % vs 4 % in the delayed and early G-CSF groups, respectively ($p < 0.0001$). The rate of fungal infection was higher in the group of patients who received delayed G-CSF ($p < 0.005$).

CONCLUSION: An early administration of G-CSF after AH SCT (on day 3 or 4) accelerates neutrophil engraftment; decreases the incidence of severe neutropenia and the risk of infectious complications (especially fungal infections) (Tab. 1, Fig. 3, Ref. 22). Text in PDF www.elis.sk

KEY WORDS: autologous HSCT, G-CSF, lymphoid malignancies, engraftment, febrile neutropenia.

Introduction

High dose chemotherapy followed by autologous hematopoietic stem cell transplantation is commonly used in the treatment of different hematological and non-hematological malignancies (3). For multiple myeloma (MM) and lymphoma patients, autologous hematopoietic stem cell transplant (HSCT) is standard of care in the treatment, demonstrating longer progression-free survival (4). One of the most common causes of mortality after hematopoietic stem cell transplantation is infection during the time of prolonged neutropenia (1–3, 5–10, 20). Prolonged neutropenia more than 7 days increases the risk of fungal infections and it is an indication for the use of antifungal prophylaxis (7, 22). After hematopoietic stem cell transplantation, granulocyte colony stimulating factor (G-CSF) is commonly used to accelerate stem cell engraftment to minimize the morbidity and mortality associated with prolonged neutropenia (1–3, 5, 7, 20). The use of granulocyte colony stimulating factor after HSCT accelerates time to neutrophil recovery

by 1–6 days when compared with control (1, 2). However, there is no consensus on the optimal timing of G-CSF after autologous HSCT, most studies have been conducted on small numbers of patients and have varied significantly in patient's demographics, G-CSF dosage regimen and other factors affecting outcomes (3, 11–19). The objective of this retrospective study is to evaluate the efficacy of early vs. delayed initiation of G-CSF after autologous HSCT in patients with lymphoid malignancies focusing on the incidence of severe neutropenia (rather than the time to neutrophil engraftment), infections, hospital stay and the overall cost.

Materials and methods

Between January 2009 and July 2014, a total of 117 patients with lymphoid malignancies (mainly multiple myeloma) who underwent autologous HSCT were included. As part of changes in the standard of care institutional protocols for autologous HSCT of myeloma and lymphoma patients in the Department of Hematology and Transfusion medicine at University Hospital Bratislava, two cohorts of patients were identified that received G-CSF (filgrastim, 5µg/kg subcutaneously) daily post-transplant until absolute neutrophil count $> 1.5 \times 10^9/L$. In the first group (43 patients), G-CSF was administered late (on day 6–8) after autologous HSCT. In the second group (74 patients), G-CSF was administered early (on day 3 or 4) after autologous HSCT. All patients received standard conditioning regimen for the underlying disease and standard

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Tab. 1. Patient's demographics and results.

	Delayed application of G-CSF	Early application of G-CSF	p
Number of patients	43	74	
Age (years)	60 (39–67)	59 (33–68)	0.694
Sex			0.079
Male; n (%)	16 (37%)	40 (54%)	NS
Female; n (%)	27 (63%)	34 (46%)	NS
Dose of CD34+cells x10 ⁶ /kg	2.5 (1.3–5.6)	2.3 (1.3–4.5)	0.138
Diagnosis			0.855
Multiple myeloma; n (%)	41 (95%)	72 (97%)	NS
NHL; n (%)	2 (5%)	2 (3%)	n.a.
ECOG performance status; n (%)			0.221
0	35 (82%)	53 (72%)	NS
1	7 (16%)	18 (24%)	NS
2	1 (2%)	2 (3%)	n.a.
3	0	0	n.a.
4	0	1 (1%)	n.a.
Engraftment of WBC (days)			<0.0001
Leu > 1 x 10 ⁹ /l	7 (4–12)	6 (3–9)	0.337
ANC > 0.5 x 10 ⁹ /l	7 (5–9)	5 (3–7)	0.036
ANC > 0.1 x 10 ⁹ /l	5 (3–6)	4 (2–6)	0.906
Engraftment of platelets >20 x 10 ⁹ /l	6.5 (3–16)	5 (3–11)	0.696
Hospitalization (days)	19 (15–28)	16 (11–23)	0.001
Severe neutropenia ≥ 7 days; n (%)	34/42 (81%)	11/66 (17%)	RR=4.8 (2.7–8.4)
Very severe neutropenia ≥ 7 days; n (%)	25/41 (61%)	2/52 (4%)	RR=15.0 (3.9–63.0)
Febrile neutropenia; n (%)	40 (93%)	64 (88%)	0.531
Invasive fungal infection; n (%)	8/43 (19%)	2/73 (3%)	0.005
HRCT scan use; n (%)	10 (23%)	4 (6%)	0.007
Overall cost (€)	3582 (787–18187)	1408 (263–2143)	0.041

HRCT – high resolution computed tomography; G-CSF – granulocyte colony stimulating factor. Values expressed in medians (range)

NS – non significant; n.a. – not applicable; RR – risk ratio (95% confidence interval); WBC – white blood cell count; ANC – absolute neutrophil count

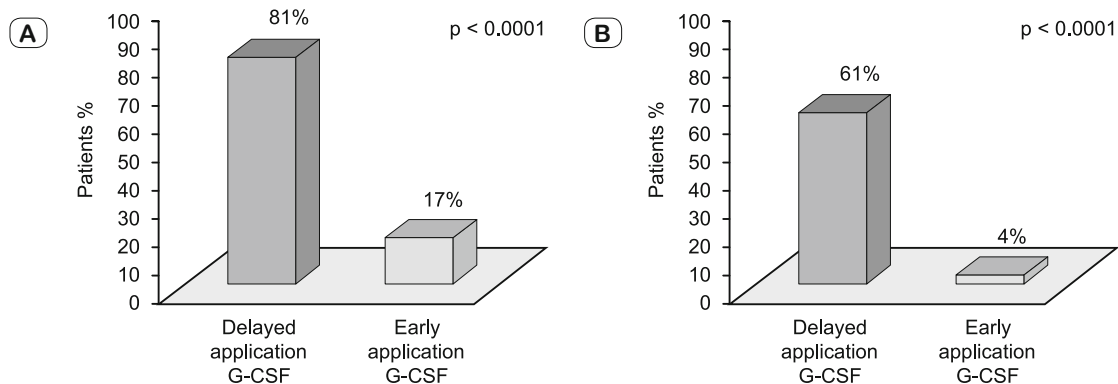


Fig. 1. Duration of neutropenia (more than 7 days). A – severe neutropenia, B – very severe neutropenia; in patients with delayed (n = 43) and early (n = 74) G-CSF administration

G-CSF – granulocyte colony stimulating factor.

supportive treatment, including treatment of febrile neutropenia. No routine antibiotic prophylaxis has been commenced. Only patients with severe mucositis received fluconazole as antifungal prophylaxis. The conditioning regimen for multiple myeloma was melphalan (200 mg/m² on day –2) and for B-cell non hodgkin's lymphoma BeAM (bendamustine, etoposide, cytarabine, mel-

phalan). Patient's demographics are shown in table 1. The primary endpoint was the incidence of severe and very severe neutropenia (lasting more than 7 days), defined as absolute neutrophil count (ANC) between 0.5–0.1 x 10⁹/L for severe neutropenia and < 0.1 x 10⁹/L for very severe neutropenia. Secondary endpoints included time to neutrophil engraftment, defined as the first of 3 consecu-

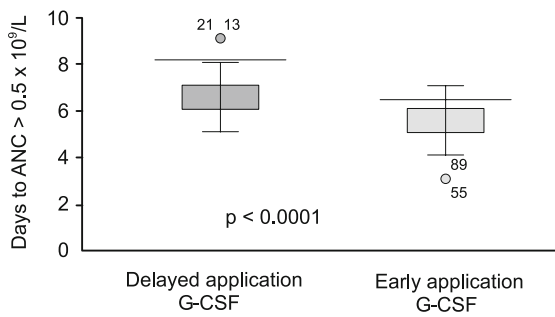


Fig. 2. Neutrophils engraftment in patients with delayed (n = 43) and early (n = 74) G-CSF administration. G-CSF – granulocyte colony stimulating factor; ANC – absolute neutrophil count.

tive days with an ANC $\geq 0.5 \times 10^9/L$, time to platelet engraftment with platelet count $\geq 20 \times 10^9/L$, incidence of febrile neutropenia, defined as the occurrence of temperature $\geq 38^\circ C$ and ANC $< 0.5 \times 10^9/L$ from day 0 to the day of ANC engraftment; incidence of fungal infection, duration of hospitalization post-transplantation from day +1 until hospital discharge and the cost of hospitalization. Statistical analysis was performed using IBM SPSS statistical software version 25, with significant p value of 0.05 (two-tailed). The Fisher exact test was used to compare categorical variables between the groups. The Mann–Whitney rank-sum test was used to compare continuous variables.

Results

No statistically significant difference was noted between the two cohorts in terms of age, gender, dose of infused CD34 cells per kg, and the conditioning regimen dose administered among the two groups of patients (Tab. 1). As shown in figure 1 the proportion of severe neutropenia for more than 7 days (ANC $< 0.5 \times 10^9/L$) in the group with delayed and a group with early G-CSF administration was 34/42 (81 %) and 11/66 (17 %), $p < 0.0001$.

Very severe neutropenia (ANC $< 0.1 \times 10^9/L$) for more than 7 days was present in 25/41 (61 %) patients with delayed and 2/52 (4 %) patients with early G-CSF administration, $p < 0.0001$. In the delayed G-CSF group the relative risk (RR) for severe neutropenia was 4.8 (95 % confidence interval 2.7–8.4) and for very severe neutropenia RR was 15 (95% confidence interval 3.9–63). Median time to engraftment of leukocytes above $1.0 \times 10^9/L$, granulocytes above $0.5 \times 10^9/L$ and granulocytes above $0.1 \times 10^9/L$ for patients who received G-CSF early was 6, 5, and 4 days, respectively and for patients who received G-CSF late 7, 7 and 5 days respectively ($p < 0.001$) (Fig. 2). The median duration of hospitalization was 19 (range 15–28) days versus 16 (range 11–23) days in the cohort of patients with delayed versus early G-CSF application ($p = 0.001$, 95% confidence interval 2.02–4.17). There was no significant difference in the rate of febrile neutropenia in both groups ($p = 0.53$), but the rate of fungal infection and the use of high resolution computed tomography (HRCT) of the lung was higher in the group of patients who received delayed G-CSF than early G-CSF (19 % vs 3 %, $p = 0.005$) and (23 % vs 6 %, $p = 0.007$) respectively (Tab. 1, Fig. 3). The cost of hospitalization was much lower in the cohort of patients how received early G-CSF ($p = 0.041$). There was no significant difference in the time to platelets engraftment between the two groups ($p = 0.69$) (Tab. 1).

Discussion

G-CSF therapy is frequently applied after autologous HSCT to optimize neutrophil recovery. Compared with placebo, G-CSF has been proven to shorten the duration of neutropenia, the length of hospital stay, and the number of infections after autologous HCST (1, 2, 5, 6). The rationale for early initiation of G-CSF after high dose chemotherapy followed by autologous hematopoietic stem cell transplantation is that the residual late-committed neutrophilic progenitors in the bone marrow early after chemotherapy can still respond to G-CSF stimulation, to temporarily increase the peripheral neutrophil count to delay the decrease of ANC and hence shorten the gap of sever neutropenia, till the late-committed

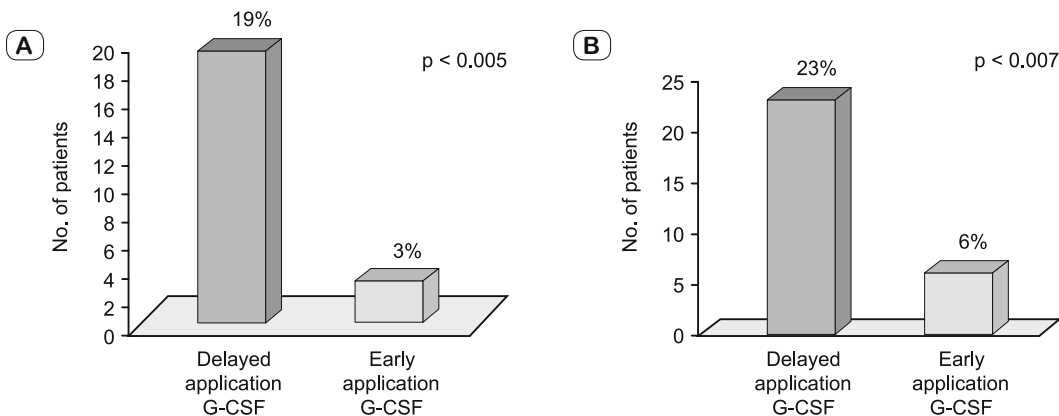


Fig. 3. The incidence of invasive fungal infection (A) and the use of HRCT of the lung (B) in patients with delayed (n = 43) and early (n = 74) G-CSF administration.

neutrophilic progenitors are formed after autologous HSCT (22). With this in mind, several studies have analyzed the optimal time to start G-CSF after autologous HSCT. However, the literature reports supporting its impact on clinical outcomes are misleading, and consensus regarding the optimal time to initiate G-CSF after HSCT is lacking (3,5, 8–17,19). Studies evaluating early versus delayed initiation of G-CSF have reported conflicting results, with some showing associations between early administration and decreased time to engraftment, length of hospital stay, and antibiotic use and others reporting no difference in outcomes when delaying G-CSF administration until day +5 (8–17, 19). The majority of these studies have been conducted on small numbers of patients and have varied significantly in patient's demographics, G-CSF dosage regimen and other factors affecting outcomes (for example the routine prophylactic use of antibiotics and antifungal drugs after HSCT), furthermore most studies were focusing on the time to neutrophil engraftment rather than the incidence and the duration of severe neutropenia (19). Evidence based guidelines provide different recommendations on the optimal time to initiate G-CSF after autologous HSCT (7, 18, 20, 21). The limited and debated data comparing the outcomes with G-CSF use as well as its optimal timing after HSCT necessitates further evaluation to determine the appropriate use of G-CSF in this setting. In addition, given the decreasing costs of G-CSF agents with the emerging availability of biosimilars, it is crucial to understand whether early initiation following HSCT confers a clinical a cost-effect benefit (5).

Here we report our institutional experience with 117 patients over 4.5-year period, including 43 patients who received G-CSF late (starting on day +6 to +8) and 74 patients who received G-CSF early (starting on day+3 / +4) after autologous HSCT. We found that there is a significantly lower rate of severe neutropenia lasting > 7 days in the group of patients who received early G-CSF compared with late G-CSF group (17 % vs 81 %, $p < 0.0001$). Risk ratio for neutropenia in the late G-CSF group was 4.8; 95% confidence interval 2.7–8.4. Outcomes from our study, which included patients with lymphoma and multiple myeloma, also demonstrated a 2-days difference in time to neutrophil engraftment in early G-CSF application ($p = 0.036$, 95% confidence interval 1.26–2.01), and 3 days shortening of hospitalization ($p = 0.001$, 95% confidence interval 2.02–4.17). Although there was no significant difference in the rate of febrile neutropenia in both groups ($p = 0.53$) the rate of fungal infection and the use of HRCT scan of the lung was higher in the group of patients who received delayed G-CSF than in early G-CSF group (19 % vs 3 %, $p = 0.005$ and 23 % vs 6 %, $p = 0.007$, respectively). It is speculated that G-CSF administration may delay megakaryocyte expansion because of the preferential proliferation of common myeloid progenitors into the neutrophils (3, 10, 11, 13–16, 18). However, in our study in accordance with the literature there was no significant difference in time to platelets engraftment between the two groups ($p = 0.696$). Limitations of this study include its retrospective design, which subjects our results to the usual restrictions and bias of this type of analyses. Nevertheless, the large size of patients groups in our study enabled us to demonstrate the

statistical significance of the endpoints assessed in this study to support an early administration of G-CSF in patients undergoing autologous HSCT.

Conclusion

We conclude that early application of G-CSF on the 3rd or 4th day after autologous HSCT (i.e. the 5th day after high dose chemotherapy) decreases the incidence of severe neutropenia, accelerates neutrophil engraftment, reduces the risk of infectious complications (especially fungal infections) and the use of prophylactic antimicrobial (antifungal) drugs, and shortens the hospital stay and overall cost of treatment. Based on the results of our study we can recommend early administration of G-CSF after autologous HSCT.

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