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ARAŞTIRMA/ORIGINAL ARTICLE

Applying G-CSF on post-transplant +5th day is advantageous on supportive treatment in patients undergoing peripheral blood stem cell transplantation

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Summary

The role of granulocyte-colony stimulating factor (G-CSF) administration on day +5 after peripheral blood stem cell transplantation in terms of hematologic engraftment and supportive treatment need has been evaluated. Forty two consecutive patients with solid and hematological malignancies were enrolled in two groups depending on G-CSF administration. Twenty seven patients were given G-CSF (5 µg/kg/day) from day +5 after the transplantation until the achievement of neutrophil engraftment. Post-transplant G-CSF was not given to the control arm of 15 patients. A number of at least $2X10^6$ $CD34^+$cells per kilogram collected by cytapheresis were given to all patients. A significant difference was found between the two groups in favor of G-CSF receiving group, in terms of neutrophil engraftment time (10.55±1.21 vs 11.93±2.89 days; p=0.04), number of days with fever (3.33±2.66 vs 5±2.95 days; p=0.03) and number of days requiring antibiotic therapy (7.07±3.46 vs 11.87±3.74 days; p<0.001), whereas no statistically significant differences were noted in terms of hospitalization period (13.30±4.79 and 13.53±2.56 days; p=0.26), platelet engraftment time (12.22±2.79 and 13.40±3.89 days; p=0.26) and erythrocyte transfusion need; however, platelet transfusion need was statistically significant between the groups with and without G-CSF support (1.27±0.96 vs 0.56±0.75, p=0.01). This study revealed that starting G-CSF on day +5 may fasten the neutrophil engraftment, decrease the number of days with fever and decrease the need for antibiotic therapy in post-transplant period.

Key words: Autologous peripheral stem cell transplantation, engraftment, G-CSF, growth factor, supportive treatment

Özet

Periferal kan kök hücre transplantasyonu uygulanan hastalarda destek tedavisinde transplant sonrası +5. günde G-CSF uygulamak avantajlıdır

Periferik kök hücre naklinden sonra +5. günde granülosit koloni stimüle edici faktör (G-CSF) uygulanmasının hematolojik engraftman ve destek tedavi gereksinimleri açılarından rolü araştırıldı. Solid ve hematolojik maligniteli 42 ardışık hasta G-CSF uygulanmasına göre iki kohort gruba ayrıldı. Yirmi yedi hastaya G-CSF (5 µg/kg/day) nakilden sonraki +5. günden nötrofil engraftmanına kadar verildi. On beş hastadan oluşan kontrol grubuna ise nakil sonrasında G-CSF verilmedi. Hastaların hepsine sitaferezle toplanan en az $2X10^6$/kg sayıda $CD34^+$ hücre verildi. Her iki grup arasında, G-CSF alan grup lehine olmak üzere nötrofil engraftman zamanı (10.55±1.21 karşın 11.93±2.89 gün; p=0.04), ateşli gün sayısı (3.33±2.66 karşın 5±2.95 gün; p=0.03) ve antibiyotik tedavisi gerektiren gün sayısı (7.07±3.46 karşın 11.87±3.74 gün; p<0.001) açılarından istatistiksel anlamlı farklılık saptandı; ancak hospitalizasyon süresi (13.30±4.79 ve 13.53±2.56 gün; p=0.26), trombosit engraftman zamanı (12.22±2.79 ve 13.40±3.89 gün; p=0.26) ve eritrosit transfüzyon ihtiyacı bakımından anlamlı farklılık saptanmadı. Trombosit transfüzyon ihtiyacı ise G-CSF desteği yapılan ve yapılmayan gruplar arasında istatistiksel açıdan anlamlı farklı bulundu (1.27±0.96 vs 0.56±0.75, p=0.01). Bu çalışma nakilden sonra +5. günde G-CSF başlanmasının nötrofil engraftmanını hızlandırdığını, ateşli gün sayısını ve antibiyotik ihtiyacını azalttığını göstermektedir.

Anahtar kelimeler: Otolog periferik kök hücre nakli, engraftman, G-CSF, büyüme faktörü, destek tedavi

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Introduction

Early hematopoietic recovery is crucial in reducing mortality and morbidity rates in patients undergoing peripheral blood stem cell transplantation (PBSCT) and defining the success of the transplantation. Many hematopoietic growth factors affect hematopoietic recovery and different administration protocols are still

under investigation in terms of the utility of growth factors to accelerate engraftment process; however the standard day on which growth factor administration should be started is not yet well defined (1-7).

Recent studies comparing early and late granulocyte-colony stimulating factor (G-CSF) administration on day +1 and +7 post-transplant revealed that early hematological engraftment achievement was not established as expected in cases with early growth factor administration (8-11).

G-CSF administration during PBSCT was shown to achieve neutrophil engraftment one week earlier approximately, but no effect on platelet engraftment and on mortality caused by infectious diseases was noted (12).

In this prospective study, we compared the two treatment groups with one receiving G-CSF on day +5 after the autologous transplantation and the other without any growth factor support. We investigated the results of the groups in terms of hematopoietic recovery and post-transplant supportive care requirements.

Material and Methods

Patients: Forty two consecutive patients were included in this interference investigation. All patients were given written informed consent form. The first group (from January 1999 to December 1999) (fifteen patients) were not given G-CSF in post-transplant period; while in the second group (from January 2000 to December 2000) twenty seven patients received G-CSF on a dose of 5 μg/kg per day, intravenously or subcutaneously from the day +5 after the infusion of stem cells until the achievement of neutrophil engraftment. All patients were informed about the study and written consent was taken from each. Patients' diagnoses were breast cancer (12 patients), osteosarcoma (4 patients), testicular cancer (6 patients), Ewing's sarcoma (2 patients), primitive neuroectodermal tumor (PNET) (1 patient), extragonadal germ cell tumor (1 patient), Hodgkin's disease (8 patients), non-Hodgkin's lymphoma (6 patients) and multiple myeloma (2 patients). (Tables I,II,III).

Cytapheresis of stem cells and cryopreservation: Stem cells were mobilized by G-CSF on a dose of 10-15 μg/kg per day subcutanously or intravenously (Filgrastim, Neupogen®, Roche, Basel, Switzerland) fourteen days after the completion of the chemotherapy. Then, apheresis was done using Cobe Spectra cell seperator (COBE Lakewood, Co, USA) after the administration of G-CSF on days 4 to 6. Apheresis was done after six to eight hours after the last dose of G-CSF. Mononuclear cells obtained by cytapheresis were then cryopreserved in liquid nitrogen at -197 °C with final concentration of 10% dimethylsulfoxide (DMSO).

Flow-cytometry: Apheresis product containing $1X10^6$ mononuclear cells per kilogram were incubated within 10 cc fluorescein isothyocyanate-conjugated anti-CD34 antibody (Becton Dickinson, Heidelberg, Germany). Isotope-identic antibodies were used as controls. A minimum of $50X10^9$/L cells were counted via flow-cytometry (FACScan, Becton Dickinson, Heidelberg, Germany) and $CD34^+$ cell number was detected thereafter.

Conditioning regimens: In patients receiving G-CSF on day +5, the conditioning regimens consisted of ICE (ifosfamide, carboplatin and etoposide) in ten patients, BEAM (BCNU, etoposide, cytarabine and melphalan) in five patients, TCM (thiotepa, carboplatin and melphalan) in one patient, CNV (cyclophosphamide, mitoxantrone and etoposide) in seven patients, melphalan in one patient, CyEAM (cyclophosphamide, etoposide, cytosine arabinoside and melphalan) in one patient, total body irradiation (TBI-12Gy/6 fr/3 days-Co60 theratron machine) with cyclophosphamide in two patients.

In the other group without G-CSF support, the regimens included ICE (4 patients), BEAM (6 patients), CNV (4 patients) and L-PAM (1 patient).

Stem cell reinfusion: The day after the completion of the conditioning regimen, the apheresis product was heated in bain-marie until 37 °C and reinfused via the central venous catheter into the patient. Diphenhydramine 50 mg and methylprednisolone 1 mg/kg were applied intravenously 30 minutes before the infusion.

Growth factor administration: In the second group who were given growth factor, G-CSF was used until the neutrophil count was over or equal $1X10^9$/L for three consecutive days.

Supportive treatment after the transplantation: Patients were stayed in isolated rooms sterilized via ultraviolet light after the stem cell infusion. Patients received ciprofloxacin per oral route for enteric decontamination prophylaxis during the neutropenic period. All patients were given the same febrile neutropenia protocol. Wide spectrum parenteral antibiotics were initiated in case of continuous fever over 38.1 °C for two hours or clinically suspected infections, after confirmation with all necessary cultures (blood cultures from both arms, and urine, stool and sputum cultures, if needed). The antibiotic treatment was changed if any pathogen was isolated microbiologically according to the antibiogram

result. If no pathogen was isolated, the initial empirical antibiotic treatment was continued until neutrophil recovery. No patient was given granulocyte infusion. Thrombopheresis was performed according to the groups. In G-CSF receiving group, platelet transfusion was given, if platelet count was under or equal to $10X10^9$/L, while in the other group not receiving G-CSF, trombopheresis was done if platelet count was under or equal to $20X10^9$/L. Erythrocyte transfusion was performed in both groups in order to establish the hemoglobin level over 8 g/dl. All blood products were transfused after irradiation with 2500 cGy dose.

Evaluation criteria: Neutrophil count over or equal 1X109/L for three consecutive days was considered as neutrophil engraftment achievement. The length of time from the reinfusion day to neutrophil engraftment was assessed as neutrophil engraftment period. Platelet count over $50X10^9$/L not requiring platelet transfusion was also assessed as platelet engraftment achievement. Days with fever were calculated according to a degree of fever over 38.1 °C. The length of time from the reinfusion of stem cells to discharge was assessed as hospitalization period. The erythrocyte or platelet transfusion needs were defined as units.

Statistical analysis: Kolmogorov-Smirnov test was used to determine the normal distribution variations of the arithmetic means and standard deviations of numerical data in the study. When data distribution was out of the normal distribution variations, Mann-Whitney U test was used to compare the means of the two groups in regard to the period between diagnosis and initiation of transplantation, numbers of pre-transplant chemotherapy courses, total nucleated cells and $CD34^+$ cells given, days with fever, time to neutrophil and platelet engraftment and erythrocyte and platelet transfusions. Chi-square test was used to determine whether any difference was present between the two groups regarding the percentage of variables of sex and radiation therapy or not. Fisher's Exact test was used if expected frequency was under 5 or sampling number was under 20. The means between the two groups regarding the length of parenteral antibiotic use were compared by t-test.

Statistical analyses were done with SPSS packet program for Windows, version 9.0, SPSS Inc. USA). $P<0.05$ level was accepted as statistically significant. Other values in the article were given as means±standard deviation.

Results

Patients: The mean age of patients not receving G-CSF and receiving G-CSF was 37±12.22 years and 32.5±12.72 years, respectively. No statistically significant differences were found in terms of age, sex, pre-transplant radiotherapy, previous chemotherapy courses and time to transplantation from diagnosis between the two groups (Table I).

Table I. Patient characteristics

Characteristics	G-CSF (day +5)	G-CSF (-)	p value
Number	27	15	
Sex (M/F)	16/11	9/6	0.963
Age (mean)	32.50±12.72	37.0±12.22	0.133
Diagnosis			
Solid tumor	18	8	
Breast cancer	8	4	
Osteosarcoma	2	2	
Testicular cancer	4	2	
Ewing sarcoma	2	0	
Primitive neuroectodermal tumor	1	0	
Extragonadal germ cell tumor	1	0	
Hematological malignancies			
Hodgkin's disease	4	4	
Non-Hodgkin lymphoma	4	2	
Multiple myeloma	1	1	
Pre-transplant radiotherapy	10	5	0.810
Previous chemotherapy courses (mean)	8.0±5.02	8.45±6.30	0.979
Conditioning regimen			
ICE	10	4	
L-PAM	0	1	
BEAM	5	6	
TCM	1	0	
CNV	7	4	
Alkeran	1	0	
CyEAM	1	0	
TBI + Cy	2	0	
Time to transplantation from diagnosis (days) (mean)	546.92±536.94	906.27±150.51	0.850
TNC ($X\ 10^8$/kg) (mean)	12.34±4.46	14.56±7.55	0.65
$CD\ 34^+$ cell number (mean)	6.23±3.93	9.30±7.83	0.25

Abbreviations: TBI: Total body irradiation, ICE: Ifosfamid, Carboplatin, Etoposide, L-PAM: Melphalan, BEAM: BCNU, Etoposide, Ara-C, Melphalan, TCM: Thiotepa, Carboplatin, Melphalan, CNV: Cyclophosphamide, Mitoxantrone, Etoposide, CyEAM: Cyclophosphamide, Etoposîde, Ara-C, Melphalan, TBI+Cy: Total body irradiation, Cyclophosphamide

Apheresis results: A total of forty two apheresis were done in two groups. In the group without G-CSF, single apheresis was done in all 15 patients, while in G-CSF receiving group, double apheresis was done in 4 patients and single apheresis was done in the remaining 23 patients. At least $2X10^6$ $CD34^+$ stem cells per kilogram were collected finally by apheresis from each patient. No statistically significant differences were detected between the two groups regarding TNC and $CD34^+$ cell counts (TNC= 14.56±7.55X10^8/kg vs 12.34±4.46X10^8/kg; p=0.65, and $CD34^+$= 9.30± 7.83X10^6/kg vs 6.23±3.93X10^6/kg; p=0.25) (Tables I,II,III).

Table II. Patient characteristics in the group not receiving G-CSF

No	Age	Sex	Diagnosis	Days with fever	Days with antib.	Erythrocyte suspension transf.	Platelet suspension transf.	Hospitaliz. period	TNC ($x10^6$/kg)	CD34 cells ($x10^6$/kg)	Conditioning regimen	Neutrophil engraftment	Platelet engraft.	Previous chemothe. courses	Previous RT	Leukaph-heresis
1	35	F	Hodgkin's	2	8	2	1	15	31.67	31.67	BEAM	15	16	8		1
2	26	M	Hodgkin's	6	7	5	4	10	14.8	3.7	BEAM	10	10	5		1
3	24	M	NHL	6	7	4	0	12	11.05	3.86	BEAM	12	13	11		1
4	28	M	Hodgkin's	5	14	2	1	14	8.96	8.06	BEAM	12	16	24	+	1
5	49	M	NHL	5	9	4	1	10	9.94	4.97	BEAM	10	10	6	+	1
6	51	F	M.myeloma	1	12	2	1	15	9	2.25	L-PAM	12	20	6	+	1
7	50	M	Hodgkin's	4	12	2	2	12	18.37	11.76	BEAM	11	12	8	+	1
8	25	M	Osteosarcoma	0	10	4	1	12	8.33	2.45	ICE	12	12	21	+	1
9	49	F	Breast cancer	7	13	3	1	13	19.87	19.87	CNV	7	7	4		1
10	22	M	Osteosarcoma	7	11	2	1	11	8.53	11.85	ICE	11	10	2		1
11	29	M	Testic. cancer	9	15	3	1	15	7.2	3.3	ICE	14	11	10		1
12	48	F	Breast cancer	10	17	3	0	15	11.28	5.98	CNV	11	12	4		1
13	45	F	Breast cancer	5	20	4	2	20	10.6	10.1	CNV	20	21	4		1
14	42	F	Breast cancer	7	14	2	1	14	27.28	7.9	CNV	10	15	4		1
15	32	M	Testic. cancer	1	9	2	2	15	21.5	11.76	ICE	12	16	10		1

Abbreviations : TNC: Total nucleated cells, RT: Radiotherapy, NHL: non-Hodgkin lymphoma; BEAM: BCNU, Etoposide, Ara-C, Melphalan; ICE: Ifosfamid, Carboplatin, Etoposide; CNV: Cyclophosphamide, Mitoxantrone, Etoposide, L-PAM: Melphalan.

Table III. Patient characteristics in the group receiving G-CSF on day +5

No	Age	Sex	Diagnosis	Days with fever	Days with antibiotic	Erythrocyte suspension (units)	Platelet suspension (units)	Days Hospitaliz.	TNC ($x10^8$/kg)	CD34 cells ($x10^6$/kg)	Conditioning regimen	Neutrophil engraft.	Platelet engraft.	Previous chemothe. courses	Previous RT	Leukaph-heresis
1	46	F	Breast ca.	5	9	2	0	13	12.20	3.78	TCM	10	8	4		1
2	56	M	NHL	1	4	2	1	15	11.08	1.10	BEAM	13	11	17	+	1
3	21	M	NHL	3	5	0	0	10	16.04	7.37	TBI+Cy	10	12	5		1
4	30	F	Breast ca.	4	7	0	0	10	9.50	9.50	CNV	10	10	8		1
5	21	M	Osteosar.	3	5	2	0	12	21.86	14.21	ICE	9	11	2		1
6	28	F	Breast ca.	1	5	0	0	14	10.78	6.14	CNV	13	11	6		1
7	52	F	M.myelo.	6	17	7	2	35	7.88	5.51	ALKERAN	10	15	4	+	1
8	46	M	Testicu.ca.	1	8	1	1	14	8.47	0.84	ICE	11	14	9		2
9	21	M	Osteosar.	6	9	4	2	10	12.10	5.56	ICE	9	11	2		1
10	23	M	Testicu.ca.	3	7	4	1	14	17.69	1.95	ICE	11	20	6	+	2
11	22	M	Hodgkin's	2	4	2	0	10	14.26	10.12	CyEAM	8	12	8		1
12	23	M	Hodgkin's	1	4	2	0	11	16.60	8.46	BEAM	10	10	9	+	1
13	56	F	Breast ca.	4	8	4	0	10	15.52	6.51	CNV	10	10	4		1
14	22	M	Extrago.tm.	5	7	6	1	14	8.70	5.39	ICE	11	12	5		1
15	24	M	PNET	5	6	0	1	11	9.25	3.88	ICE	9	10	5	+	1
16	23	F	Hodgkin's	0	0	2	0	12	13.23	4.10	BEAM	11	14	23	+	1
17	29	F	Breast ca.	2	9	3	0	14	9.87	2.36	CNV	12	13	10	+	1
18	19	F	NHL	3	7	2	0	12	9.00	2.00	BEAM	11	18	12	+	2
19	28	F	Breast ca.	3	10	0	1	14	19.55	2.70	CNV	11	13	7		1
20	23	M	NHL	6	10	0	0	13	5.52	7.39	TBI+Cy	11	12	4		1
21	35	M	Hodgkin's	1	6	2	0	14	9.90	13.20	BEAM	11	15	14	+	1
22	52	F	Breast ca.	4	7	2	0	12	12.20	10.37	CNV	11	9	4		1
23	42	F	Breast ca.	4	8	2	0	12	6.29	11.90	CNV	10	9	4		1
24	21	M	Ewing sarc.	0	0	2	0	8	13.20	8.05	ICE	10	11	16	+	1
25	46	M	Ewing sarc.	3	7	2	1	13	6.50	1.95	ICE	9	10	6		1
26	46	M	Testicu. tm.	13	13	4	2	17	14.62	2.03	ICE	12	13	12		2
27	23	M	Testicu. tm.	1	9	2	2	15	21.50	11.76	ICE	12	16	10		1

Abbreviations : NHL: Non-Hodgkin lymphoma ; BEAM: BCNU, Etoposide, Ara-C, Melphalan; ICE: Ifosfamide, Carboplatin, Etoposide; CNV: Cyclophosphamide, Mitoxantrone, Etoposide, PNET: Primitive Neuroectodermal Tumor, TCM: Thiotepa, Carboplatin, Melphalan, TBI+CV: Total Body Irradiation, Cyclophosphamide, CVEAM: Cyclophosphamide, Etoposide, Ara-C, Melphalan

Table IV. Engraftment and supportive care findings

Clinical parameters	G-CSF (-)	G-CSF (day +5)	p value
Neutrophil engraftment ($1X10^9$/L)	11.93±2.89	10.55±1.21	0.04
Platelet engraftment ($50X10^9$/L)	13.40±3.89	12.22±2.79	0.31
Days with fever (>38.1°C)	5.0±2.95	3.33±2.66	0.03
Days with antibiotics	11.87±3.74	7.07±3.46	<0.001
Erythrocyte suspension transfusion (units)	2.93±1.03	2.18±1.78	0.05
Platelet suspension transfusion (units)	1.27±0.96	0.56±0.75	0.01
Post-transplant hospitalization (days)	13.53±2.56	13.30±4.79	0.26

Neutrophil and platelet engraftment: In patients receiving and not receiving G-CSF, neutrophil engraftment was achieved on days 10.55±1.21 and 11.93±2.89, respectively. In the first group with G-CSF, the engraftment was faster than the other group, revealing a statistical significance (p=0.04). Furthermore, in patients receiving and not receiving G-CSF, platelet engraftment was achieved on days 12.22±2.79 and 13.40±3.89, respectively. Two groups revealed no statistically significant differences for platelet engraftment (p=0.31) (Table IV).

Supportive care findings: Number of days with fever and days requiring antibiotic treatment were significantly lower in G-CSF receiving group than without G-CSF group with 3.33±2.66 vs 5±2.95 days; p=0.03 and 7.07±3.46 vs 11.87±3.74 days; p<0.001, respectively.

Post-transplant erythrocyte suspension transfusion need was similar in both groups (2.18±1.78 vs 2.93±1.03 units; p=0.05); however, platelet suspension transfusion need was lower in G-CSF receiving group in post-transplant period (0.56±0.75 vs 1.27±0.96 units; p=0.01).

The length of hospitalization after the completion of transplantation was similar in both groups (13.30±4.79 days in G-CSF receiving group vs 13.53±2.56 days in the group not receiving G-CSF; p=0.26) (Table IV).

Discussion

Although some studies reveal no benefit of growth factors for neutrophil engraftment, many others suggest that hematopoietic growth factors accelerate neutrophil engraftment, shorten number of days with fever and antibiotic use (1-7). In our study, we aimed to compare the two groups receiving and not receiving G-CSF in post-transplant period and analyzed the results of engraftment as well as supportive needs between the two groups.

Ojeda et al. randomized 62 patients with advanced stage breast cancer, lymphoma and acute myeloid leukemia into two groups. One group received G-CSF from day +5 after the transplantation and the other group received no growth factors (13). They reported that the neutrophil engraftment was faster in G-CSF receiving group (12 days vs 10 days, p=0.0008); however, platelet engraftment was not changed (p=0.11) and no significant difference was noted between the groups regarding days with fever, number of infections and supportive care requirements.

Azevedo et al. randomized 87 patients into two groups in a multicenter study. In one group they gave G-CSF on 5 μg/kg/day dose from the first day after the transplantation and in the second group they started the same dose of G-CSF on the 5th day after the infusion until neutrophil engraftment (14). The period with neutropenia was shorter in patients who received G-CSF starting on the first day. No significance was noted in Azevedo's study between the two groups regarding either the neutrophil and platelet engraftment time and days with fever.

On the other hand, Hornedo et al. investigated the role of post-transplant G-CSF administration in breast cancer cases (15). They randomized the patients into three groups. They gave G-CSF at 5 μg/kg/day dose on the 0th day to the first group and on the 5th day to the second group, whereas the third group has received no growth factor. When compared, neutrophil engraftment was achieved earlier in growth factor supported group (p=0.001). The extent of hospitalization was relatively shorter in patients who received G-CSF. Although neutrophil engraftment was achieved earlier in the first group than in the second group, days with fever, hospitalization duration, platelet engraftment, erythrocyte or platelet requirements were found statistically insignificant. In fact, the investigators have recommended administering G-CSF on day +5 as a standard practice.

We revealed in the current study that neutrophil engraftment was faster in G-CSF administered patients on day +5 in post-transplant period. Our findings are consistent with the results of the study of Ojeda et al. in terms of neutrophil engraftment (11.93±2.89 vs 10.55±1.21 days; p=0.04) and platelet engraftment

(13.40±3.89 vs 12.22±2.79 days; p=0.315). Significant decrease in days with fever and antibiotic use in our study may result from early neutrophil engraftment achievement. On the other hand, platelet engraftment was similar in both groups (13.40 vs 12.22 days; p=0.31). Patients required more platelet transfusion in the group not administered G-CSF compared with the group given G-CSF (1.27 vs 0.56; p=0.01), which may be due to the threshold accepted for platelet transfusion to be $20X10^9$/L in the first (without G-CSF support) than the other group where the threshold for thrombopheresis was set to be $10X10^9$/L.

In conclusion, we suggest that cases undergoing PBSCT with $CD34^+$ cell number over or equal to $2x10^6$/kg and with G-CSF support on day +5 have faster neutrophil engraftment, shorter period of days with fever and also antibiotic use. Nevertheless, our findings as regards of hospitalization duration, erythrocyte and platelet transfusion requirements are similar in both G-CSF supported and not supported groups. In fact, starting G-CSF administration on day +5 will therefore reduce post-transplant cost due to the growth factor use and seems therefore to be a rational approach.

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