RESEARCH COMMUNICATION

Factors Affecting Engraftment Time in Autologous Peripheral Stem Cell Transplantation

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Abstract

Background: Rapid hematological engraftment at autologous peripheral stem cell transplantation (APSCT) is a significant factor in reduction of early transplant-related complications and costs. For this reason, it is important to determine influences on hematological recovery. Methods: This study was designed to evaluate factors affecting leukocyte and platelet engraftment times after high dose chemotherapy following APSCT. A total of 228 patients (131 males and 97 females) were enrolled. Results: There were statistically significant differences between patients with $CD34^+$ cell doses $\geq 2.5\times10^6$/kg (n=180) and $<2.5\times10^6$/kg (n=48), regarding leukocyte engraftment at 11 and 12 days, respectively ($p<0.02$), between G-CSF (n=167) and GM-CSF (n=61) posttransplant regarding median leukocyte engraftment times ($p=0.005$), and between with (n=75) or without (n=153) history of pretransplant radiotherapy for both leukocyte and platelet engraftment times ($p<0.001$). Conclusions: For leukocyte engraftment, a history of pretransplant radiotherapy, type of growth factor used and number of $CD34^+$ cells infused, and for platelet engraftment, a history of pretransplant radiotherapy were found to be independent variables on multivariate analysis with the Cox regression method.

Keywords: autologous peripheral stem cell transplantation - engraftment time - $CD34^+$ cells - G-CSF - GM-CSF

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Introduction

Autologous peripheral stem cell transplantation (APSCT) is an alternative treatment for lymphoma, leukemia and some solid tumors. APSCT has resulted in substantial survival advantage for patients with multiple myeloma and relapsed high-grade lymphomas. APSCT is associated with faster hematological engraftment, less erythrocyte and platelet transfusions, fewer febrile days, less antibiotic use and treatment related costs compared to bone marrow transplantation (Hartmann et al., 1997; Bolwell et al., 1998; Le Corroller et al., 1998; Ketterer et al., 1998; Pecora et al., 1998). Besides, the risk for tumor contamination is lower in APSCT than autologous bone marrow transplantation (Henon et al., 1992).

A successful APSCT can only be achieved through eradication of the underlying disease and complete engraftment of the bone marrow. Fast hematological engraftment is a significant factor in reduction of early transplant related complications and costs (Henon et al., 1992; To et al., 1992). For this reason, it is important to determine the factors affecting hematological recovery. In the present retrospective study, we aimed to evaluate the effects of some factors on hematological engraftment in patients who underwent APSCT in our adult transplantation center.

Materials and Methods

Patients

Between June 1997 and July 2004, 228 patients with solid (n=128) or hematological (n=100) malignancies who were underwent APSCT in the our bone marrow transplantation (BMT) center were included the study. The most frequent five diagnosis were breast cancer (n=68), non-Hodgkin's lymphoma (n=42), Hodgkin's disease (n=31), osteosarcoma (n=24), testicular cancer (n=17) Patients characteristics are shown in Table 1. Written consent to participate for APSCT was obtained from all patients prior to initiation of APSCT program.

Collection of peripheral blood stem cells

Fourteen days after the last induction chemotherapy, stem cells were mobilized by using G-CSF (Neupogen®. Roche) (10-15μg/kg per day 2 h infusion) for 4-6 days. The leukapheresis procedure was caried out by COBE Spectra (COBE Lakewood. CO USA). The mononuclear cells obtained were cryopreserved in such a way that the final dimethyl sulfoxide (DMSO) concentration was 10% . After completion of the preparation regimen the product was heated to 37° C and intravenously infused. For premedication 50 mg of diphenhydramine and 1 mg/kg methylprednisolone were administered.

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Table 1. Patient Characteristics

Age median (range) years	31,5 (13-70)
Sex (male/female)	131/97
Disease (n)	
Solid tumors	128
Hematological tumors	100
Preparation regimen (n)	
ICE	84
BEAM	49
CNV	44
Others	51
$CD34^+$ cell count (n)	
<2,5 x 10^6 per kg	48
≥2,5x 10^6 per kg	180
Growth factor (n)	
G-CSF	167
GM-CSF	61
Irradiation* (n)	
Yes	75
No	153

ICE (Ifosfamide, Carboplatin, Etoposide), CNV (Cyclophosphamide, Mitoxantrone, Etoposide), BEAM (BCNU, Etoposide, Ara-C, Melphalan). G-CSF (Granulocyte Colony Stimulating Factor), GM-CSF (Granulocyte Macrophage Colony Stimulating Factor); *Irradiation prior to autologous PSCT

Preparative regimens

In the autologous PSCT, the following conditioning regimens were administered: ICE (Ifosfamide 15g/m^2, Carboplatin 1,5g/m^2, Etoposide 1,5g/m^2 in divided doses in 6 days) to 84 patients; CNV (Cyclophosphamide 2.4g/m^2/day, Mitoxantrone 35mg/m^2/day and Etoposide 1.5g/m^2 in divided doses in 6 days) to 44 patients: BEAM (BCNU 300 mg/m^2/day, Etoposide 200mg/m^2/day x 4 days, Ara-C 200 mg/m^2/day x 4 days, Melphalan 140mg/m^2/day) to 49 patiens.

Post-transplant haematopoietic growth factors

All patients who rested for one day following the conditioning regimens received the harvested product by infusion. In order to accelerate the engraftment in the post-transplant period for 167 patients 5μg/kg per day G-CSF (Neupogen® Roche) and for 61 patients 5μg/kg per day GM-CSF (Leucomax® Novartis) were given by 2 h infusion. The haematopoietic growth factor was started on day 1 and continued until three more days after leukocyte count reached > 1 x 10^9 per L. Leukocyte engrafment was defined as the first of 3 consecutive days with a sustained leukocyte count of 1 x 10^9 per L. Platelet engrafment was defined as the first day of three consecutive platelet counts unsupported by transfusion of 20x10^9 per L.

Post-transplant supportive treatment

After infusion, patients were isolated in conventional rooms with ultraviolet light and laminar airflow. Low bacterial diet, oral antibiotic for enteral decontamination and total parenteral nutrition were given to all patients. In the event of fever above 38° C lasting more then 2 h or if infection was suspected clinically blood samples were taken and wide spectrum antibiotics were initiated. The antibiotic treatment was readjusted according to the microbiological culture results. To keep the haemoglobin level above 8g/dl or the platelet count above 20 x 10^9 per L, erythrocyte or platelet transfusions were administered. In all cases blood products were irradiated with 25 Gy.

Statistical Analysis

Results are expressed as median and range. Differences between groups were tested for significance by Mann-Whitney U test. Log-rank tests were used to assess differences in engraftment rate. Cox regression analysis was used to determine independent predictors. Relationships between variables was analyzed by Pearson's correlation. Differences and correlations were considered significant at $p< 0.05$. Statistical analyses were performed with SPSS 10.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA).

Table 2. Factors that were Investigated the Effects on Leukocyte and Platelet Engraftments

Characteristics	Leukocyte engraftment time		Platelet engraftment time	
	Median (range)	p value	Median (range)	p value
$CD34^+$ cell count				
<2,5 x 10^6 per kg	12 (9-24)	0.020	14.5 (10-52)	0.25
≥2,5 x 10^6 per kg	11 (4-40)		14 (3-60)	
Preparation regimen				
ICE + CNV	11 (7-44)	0.003	14 (3-38)	<0.001
BEAM	11 (7-28)		15 (7-52)	
Growth factor				
G-CSF	11 (4-24)	0.005	14 (3-60)	0.32
GM-CSF	12 (7-40)		14 (5-44)	
Radiotherapy*				
Yes	12 (6-40)	<0.001	16 (9-60)	<0.001
No	11 (4-28)		13 (3-52)	
Sex				
male	11 (6-40)	0.04	14 (3-60)	0.001
female	11 (4-24)		13 (4-27)	
Disease				
Hematological malignancies	11 (6-40)	0.006	15 (3-60)	<0.001
Solid tumors	11 (4-24)		13 (4-27)	

ICE (Ifosfamide, Carboplatin, Etoposide), CNV (Cyclophosphamide, Mitoxantrone, Etoposide), BEAM (BCNU, Etoposide, Ara-C, Melphalan). G-CSF (Granulocyte Colony Stimulating Factor), GM-CSF (Granulocyte Macrophage Colony Stimulating Factor); *Irradiation prior to autologous PSCT.

Results

In all the patients, median of leukocyte engraftment time was 11 days (range 4-40) and median of platelet engraftment time was 14 days (range 3-60). In patients with hematological malignancies (n=100) and solid tumors (n=128), median of leukocyte engraftment time were 11 days (range 6-40) and 11 days (range 4-24) ($p<0.006$), and that of platelet engraftment 15 days (range 3-60) and 13 days (range 4-27) ($p<0.001$), respectively.

Between patients with $CD34^+$ cell dose $\geq 2.5\times10^6$/kg (n=180) or $<2.5\times10^6$/kg (n=48), there was statistically significant difference regarding leukocyte engraftment 11 (range 4-40) and 12 (range 9-24) days, respectively, ($p<0.02$), but no difference regarding platelet engraftment 14 (range 3-60) and 14.5 (range 10-52) days, respectively; ($p=0.25$) as shown in Table 2.

Between patients receiving G-CSF (n=167) or GM-CSF (n=61) posttransplant, significant difference was noted regarding median of leukocyte engraftment times 11 (range 4-24) and 12 (7-40) days, respectively; ($p=0.005$) but no difference regarding platelet engraftment 14 (range 3-60) and 14 (5-44) days, respectively; ($p=0.32$).

Leukocyte engraftment time was shorter in female compared to male 11 (range 4-24) and 11 (range 6-40) days, respectively; ($p=0.04$) and platelet engraftment time was shorter in female too 13 (range 4-27) and 14 (range 3-60) days, respectively; ($p<0.001$). But after exclusion of cases with breast cancer and testicular cancer, between female (n=29) and male (n=114) there were no differences regarding leukocyte and platelet engraftment time ($p=0.26$ and $p=0.58$, respectively).

Between patients with (n=75) or without (n=153) histo ry of pretransplant radiotherapy, there were significant differences regarding both leukocyte engraftment 12 (6-40) and 11 (4-28) days, respectively; ($p<0.001$) and platelet engraftment 16 (range 9-60) and 13 (3-52) days, respectively; ($p<0.001$).

Patients were divided into subgroups according to preparative regimens. Subgroups with ICE (n=84), CNV (n=44), and BEAM (n=49) were compared with each other regarding engraftment times. At least one group was different from the others regarding leukocyte engraftment ($p=0.003$). The fastest leukocyte engraftment time was noted in the ICE group, and the slowest in the BEAM group. At least one group was different from the others regarding platelet engraftment ($p<0.001$). The fastest platelet engraftment time was noted in the CNV group, and the slowest in the BEAM group. After merging ICE and CNV groups (both are used in solid tumors), we found that between the subgroup ICE+CNV (n=128) and BEAM (n=49)(used in heamatological malignancy), there was significant difference regarding leukocyte engraftment time 11 (7-44) and 11 (7-28) days, respectively, ($p=0.003$). In ICE+CNV group platelet engraftment was faster if compared with BEAM group 14 (3-38) and 15 (7-52) days, respectively; ($p<0.001$).

In patients receiving $CD34^+$ cells $\geq 2.5\times10^6$/kg or $<2.5\times10^6$/kg, there were no differences regarding number of febrile days (4 and 4 days, respectively; $p=0.83$) and number of days on parenteral antibiotherapy (8 and 10 days, respectively; $p=0.10$). Mild but statistically significant correlations were noted between leukocyte engraftment time and number of febrile days ($r=0.261$, $p<0.001$) and also between leukocyte engraftment time and number of days on parenteral antibiotherapy ($r=0.27$, $p<0.001$). Correlations between platelet engraftment time and number of febrile days ($r=0.29$, $p<0.001$) and also platelet engraftment time and number of days on parenteral antibiotherapy ($r=0.39$, $p<0.001$) were significant.

For variables that were found to be obviously statistically significant or vaguely significant but clinically important in univariate analysis, multivariate analysis with Cox regression method was applied. In multivariate analysis, growth factor administered posttransplant, history of pretransplant radiotherapy, and number of $CD34^+$ cells infused were found to be independent variables for leukocyte engraftment whereas history of pretransplant radiotherapy were found to be independent variables for platelet engraftment.

Discussion

Rapid hematological recovery after APSCT is associated with diminished rate of infections, shorter hospital stay and diminished transplant related costs. Various factors such as the underlying diagnosis, preparative regimen, history of pretransplant radiotherapies and chemotherapies may influence engraftment rate. Numerous studies have demonstrated that rapid hematological reconstitation depends on the number of $CD34^+$ cells (Gordon et al., 1995; Bensinger et al., 1996). In our study we found that infusion of $CD34^+$ cells $\geq 2.5\times10^6$/kg is associated with faster leukocyte engraftment. But platelet engraftment did not differ between groups with $CD34^+$ cell dose over or under 2.5×10^6/kg. Diaz et al (1996) reported significant correlations between $CD34^+$ cell dose and both leukocyte and platelet engraftment times. Similarly Weaver et al. (1995) confirmed this finding. They showed that there was a clear dose-response relationship between the number of $CD34^+$ cells and neutrophil and platelet engraftment kinetics. The $CD34^+$ cell dose of 2.5×10^6/kg is accepted as threshold level for optimum engraftment (To et al., 1997; Ketterer et al., 1998; Gandhi et al., 1999; Villaon et al., 2000;), and also higher doses were shown to be associated with faster hematological recovery (Weaver et al., 1995; Ketterer et al., 1998). And it was demonstrated that a significantly delayed neutrophil engrafment was observed in patients with doses of $CD34^+$ cells lower than 2×10^6/kg (Kudo et al., 2005).

The positive effects of growth factors on the hematological recovery are the consequens of different pathways such as neutrophil production, differentiation and proliferation (Sheridan WP et al., 1989). It is unclear whether one of the growth factors preparation offers a better clinical benefit after APSCT. We found that leukocyte engraftment is faster in patients who received G-CSF in the posttransplant period, compared to those who received GM-CSF, which is consistent with the study of Jansen et al (1999). However, Zumberg et al (2002) reported that neutrophil engraftment did not differ between patients receiving G-CSF or GM-CSF. Between G-CSF

and GM-CSF groups we found significant difference regarding leukocyte engraftment but no difference regarding platelet engraftment. Keever-Taylor et al (2001) reported faster neutrophil engraftment but delayed platelet engraftment in patients receiving G-CSF after bone marrow transplantation. After APSCT filgrastim was found to significantly reduce duration of neutropenia, thrombocytopenia as compared to lenograstim in a retrospective analysis of adult patients (Kim et al., 2003). However, Huttmann et al (2005) reported that filgrastim and lenograstim were equally effective on the hematological recovery

The timing of growth factor administration after APSCT is controversial. G-CSF has been usually started on the day of stem cell infusion. Colby et al (1998) reported shorter hospitalization and lower use of IV antibiotics when G-CSF was started on day +1 instead of day +4. Similarly a retrospective study suggested that patient who start G-CSF support on day of transplant have faster engrafment than patients who start G-CSF support on the +5 day after transplant (Thompson et al., 2009). However, others have reported that delayed administration of myeloid growth factor leads to similar engrafment time and results in cost savings (Faucher et al., 1996; Bolwell et al., 1998).

In all patients, irrespective of the underlying diagnoses, leukocyte and platelet engraftment is faster in women. However after exclusion of cases with breast and testicular cancer, gender does not seem to influence the hematological engraftment, which means that diagnosis rather than gender is associated with engraftment. De Rosa et al (2004) showed that a significantly prolonged time for neutrophil recovery was needed in myeloma patients, compared with breast cancer patients after APSCT whereas time for platelet recovery were not different. Martin et al (1998) observed shorter hematologic recovery times for breast cancer patients than the patients with hematologic malignancies. Similarly we have observed a more rapid hematologic recovery in patients with solid tumors than in patients with hematologic malignancies. The reason of delayed engraftment in patients with hematological malignancies may be associated more chemotherapy cycles prior to transplantation. Delayed leukocyte and platelet engraftments in patients who had received radiotherapy before transplantation, may be associated with disordered bone marrow microenvironment due to radiotherapy.

In our study, the fastest leukocyte engraftment was noted in patients receiving ICE, and the fastest platelet engraftment in those receiving CNV. Leukocyte and platelet engraftments were the slowest in those receiving BEAM. Since ICE and CNV were mainly used for solid tumors and, BEAM was used for heamotological malignancies, it is not clear that which one more related to engraftment underlying diagnosis or conditioning regimen. After merging ICE and CNV groups, we found that in the subgroup ICE+CNV, leukocyte and platelet engraftments were faster than in the BEAM group. Cetkovsky et al (2000)reported increased infectious complications in patients receiving BEAM, which is indirectly consistent with our findings.

We found mild but meaningful correlations between numbers of days with fever, number of days on parenteral antibiotherapy, and both leukocyte and platelet engraftment rates. In patients with $CD34^+$ cell dose $\geq 2.5\times10^6$/kg, number of febrile days and number of days on parenteral antibiotherapy were lower if compared to patients with $CD34^+$ cell dose $< 2.5\times10^6$/kg, however, this difference was not statistically significant. Ashihara et al.(2002) reported neutrophil engraftment was faster in patients with $CD34^+$ cell dose $\geq 5\times10^6$/kg than patients with $CD34^+$ cell dose $< 5\times10^6$/kg, but there was no significant difference in number of febrile days and number of days on parenteral antibiotherapy between any two groups. But Scheid et al (1999) showed that infectious complications and parenteral antibiotic use diminished in patients with $CD34^+$ cell dose $>5\times10^6$/kg. The results of studies were different. The role of the underlying disease on the incidence of infection was analysed by Sezer et al (2000) of 100 patients with lymphoma and breast cancer. They reported a significantly higher infections in patient with lymphoma. A lower incidence of infection after autologous bone marrow transplantation was noted in patients with breast cancer (Barton et al., 2001). De Rosa et al (2004) reported that a significantly higher incidence of bacterial infections in myeloma patient than breast cancer patient. In the myeloma patients the delayed engrafment of neutrophils may have been responsible for the higher incidence of early infection.

Our study was conducted in a single center and included patients with the same supportive care program, which is its powerful side. But the study heterogenous regarding diagnosis, therapies before transplantation, preparative regimens, which is its weak side.

Our multivariate findings showed that number of $CD34^+$ cells reinfused, posttransplant growth factor administration, and history of pretransplant radiotherapy influences leukocyte engraftment time whereas history of radiotherapy influence platelet engraftment time. Engraftment time is associated with transplant related morbidity and mortality, that is why further prospective studies in homogenous groups with more patients and longer follow-up are needed.

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