



Adverse Events after Infusion of Cryopreserved and Non Cryopreserved Hematopoietic Progenitor Cells from Different Sources

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Abstract

Hematopoietic Stem Cell (HSC) transplantation from different sources is mainly used for treatment of life-threatening hematopoietic malignancies. Infusion of thawed hematopoietic HSC may produce a variety of Adverse Events (AEs) usually mild to moderate. The most frequent AEs reported include nausea, vomiting, headache, diarrhoea, flushing, chills, and fever. Our objective was to analyse in a prospective way the AEs occurring in our Transplantation Unit and related to the infusion of HSC from different sources and in different conditions. We have prospectively collected data on adverse events occurring after 126 infusions of HSC performed in our Transplantation Unit between January 2016 and December 2016. Autologous peripheral blood and cord blood HSC were Cryopreserved using DMSO. Before infusion the grafts were automatically washed with a solution containing albumin, Acid Citrate Dextrose (ACD) and dextran. Allogeneic peripheral blood was infused shortly after collection. For a 1-year period 126 patients received high dose chemotherapy followed by infusion of HSC grafts: 60 patients received thawed and washed autologous peripheral blood HSC, 52 patients received allogeneic non-manipulated HSC and 14 patients received thawed and washed umbilical cord blood grafts. Infusion related AEs were reported in 41 patients (32.5%): 39 were graded 1, and two were graded 2. Median time of AEs appearance was 5 hours after infusion. More than one AE was reported in 26 patients (20.6%). Patients who suffered an AE were older than patients who did not ($p=0.059$). Despite the HSC grafts washing, AEs after infusion occurs in a significant number of patients.

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Introduction

Hematopoietic progenitor cell transplantation from bone marrow, peripheral blood and cord blood is mainly used for treatment of life-threatening hematopoietic malignancies, immunological and congenital diseases. The use of peripheral blood or cord blood instead of bone marrow has been established in clinical transplantation routine [1]. The Hematopoietic Progenitor Cells (HPC) can be stored and infused in different ways according to the source and transplantation modality and schedule. HPC from autologous peripheral blood and cord blood are usually Cryopreserved using Di-Methyl-Sulphoxide (DMSO) with a final concentration of 10%, and stored in gas or liquid nitrogen [2]. Allogeneic peripheral blood is not usually cryopreserved but kept at room temperature or refrigerated and infused immediately after collection without further manipulation. Infusion of thawed hematopoietic stem cell grafts may produce a variety of Adverse Events (AEs) usually mild to moderate. The most frequent AEs reported in previous studies include nausea, vomiting, headache, abdominal cramps, diarrhoea, flushing, chills, and fever as [3]. These complications have been mainly related to DMSO that is usually infused with progenitor grafts [4]. Other factors that have been related to the AEs are damaged cells, the amount of granulocytes, the red blood cell content and free hemoglobin in the apheresis product [5-9]. In order to overcome the negative effects, some Transplantation Centers remove the DMSO before infusion by washing the progenitor cells [2]. However, non-manipulated peripheral blood HPC can also produce adverse events [10]. The objective of our study was to analyze in a prospective way the adverse effects occurring in our Transplantation Unit and related to the infusion of HSC from different sources and in different conditions.

Table 1: Characteristics of patients and grafts according to whether they developed or not AE.

Patient characteristics	Adverse events after HSC infusion		p
	YES	NO	
N	41	85	
Age median (range)	53 (5-70)	45 (1-70)	0.059
Sex (male/female)	29/12	55/30	0.506
Diagnosis			
Acute leukemia	15	40	
Lymphoma	11	9	
Multiple myeloma	10	17	0.334
Steroids before infusion (Yes/no)	14/27	44/40	0.090
Graft characteristics			
Volume infused (ml)	356 (95-600)	274 (100-1299)	0.175
TNC* x 10 ⁹	7 (1-84)	4 (0.6-45)	0.205
Time of infusion (min)	100 (20-320)	75 (15-210)	0.062
Autologous/allogeneic	25/16	35/49	0.081
Fresh/thawed	13/28	37/47	0.513
Cord blood/peripheral blood	4/37	10/74	0.880

*Total nucleated cells

Material and Methods

Patients

We have prospectively collected data on adverse events occurring after 126 infusions of HSC performed in our Transplantation Unit between January 2016 and December 2016. The infused HSC were from two different sources: cord blood and peripheral blood. The Peripheral Blood Progenitor Cells (PBPC) were collected by apheresis after mobilization with granulocyte colony-stimulating factor (rHuG-CSF; filgrastim, Amgen, Thousand Oaks, CA) alone (10 µg/Kg) or following different chemotherapy regimens and 5 µg/Kg rHuG-CSF. The Harvest started the fifth day of treatment for those patients receiving only rHuG-CSF, if at least 10 CD34⁺/µ cells per microliter were present in the peripheral blood sample for autologous PBPC. Collection after chemotherapy mobilization was performed the day in which at least 10 CD34⁺/µl cells count was reached in peripheral blood. For this purpose, CD34⁺ cells were counted daily. PBPC were collected on a continuous-flow blood cell separator (COBE Spectra cell separator, Gambro BCT, Lakewood, CO, USA). A mean of two blood volumes was processed. Consent was obtained prior to the procedure from all patients following institutional guidelines. Compatible cord blood units were requested to the origin cord blood bank and stored in the Regional Transfusion Centre until thawing.

Processing and Infusion of hematopoietic progenitor cells

After collection, Autologous Peripheral Blood Progenitor Cells (APBPC) was sent to the Regional Transfusion Centre for cryopreservation and storage until transplantation. Cryopreservation was performed by adding DMSO in a final concentration of 10 % using a controlled rate freezer. For thawing, the frozen bags (peripheral blood or cord blood) were placed in a 37 °C water bath. The hematopoietic cells were washed with a solution containing albumin, Acid Citrate Dextrose (ACD) and dextran solution in an IBM-COBE 2991 cell processor (Gambro BCT, Lakewood, CO, USA) as described previously [11]. Cord blood was also thawed and washed in the same way. Allogeneic peripheral blood from related or non-related donors was infused shortly after collection or reception in the transplantation Centre, without any graft manipulation. The infusion was performed directly from bags and by gravity. Before HPC infusion,

premedication consisting of diphenhydramine 50 mg for autologous grafts and diphenhydramine 50 mg + methyl-prednisolone 20-40 mg for allogeneic grafts were administered 30-60 minutes before starting the infusion. Appearance of Adverse Effects (AE) was collected in a prospective way. Type (chills, fever, vomiting, skin rash, diarrhoea, abdominal pain, dyspnea, and headache), grade and number of AEs were recorded by blood bank staff using a specifically designed worksheet. AE occurring during the 24 hours after graft infusion were recorded and graded according to the CTC-NCI classification [8]. Care of the patients during infusion was performed by the physician. We consider that 24 hours is a reasonable time to collect the most important adverse effects related to the HPC infusion. If the physician responsible for the patients detects a posterior adverse effect that could be related to the HPC infusion, they inform the blood bank.

Statistical analysis

Computer software SPSS (version 15, SPSS Inc., Chicago, IL) and R (version 2.1.2.2, the CRAN project) were used to perform the statistical analysis. Descriptive statistics are presented for variables. The Kolmogorov-Smirnov test was employed to investigate the normal distribution of the variables. Results are expressed as mean ± S.D, or median and range for continuous variables and as numbers with percentages for categorical variables. Categorical variables were compared by means of the Chi square test or the Fisher exact test. The Mann-Whitney U-test or the Kruskal-Wallis tests for continuous variables were used to compare the groups when applicable. Multiple logistic regressions were used to investigate the risk factors on AEs after HPC infusion. The multivariable analysis included patient characteristics: age, sex, ABO matching (identical, minor and major), diagnosis, steroids in premedication, and graft characteristics: total nucleated cells (TNC) x 10⁹, volume, time of infusion, allogeneic versus autologous, Cryopreserved versus non-Cryopreserved, cord blood versus peripheral blood. A p value of <0.05 was considered significant.

Results

For a 1-year period 126 patients received high dose chemotherapy followed by infusion of HPC grafts: 60 patients received thawed and washed APBPC, 52 patients received allogeneic non-manipulated

Table 2: Adverse events.

Adverse events	n
Non-cardiovascular events	
Nausea/vomiting	22
Fever	15
Chills	13
Skin rash and/or pruritus	12
Abdominal pain	9
Dyspnea	2
Cardiovascular events	
Hypertension	1

PBPC and 14 patients received thawed and washed umbilical cord blood grafts. Median age of patients was 46 years (range 1-70). Sixty-seven patients received only diphenhydramine before infusion to prevent symptoms, while the rest of patients received diphenhydramine plus methyl-prednisolone. Median and range of infused volume and time of infusion were 305 ml (95-1299) and 80 minutes (15-320), respectively. Infusion related AE were reported in 41 patients (32.5 %): 39 were graded 1, and two were graded 2. Median time of AE appearance was 5 hours after infusion. In 12 patients adverse events appeared within the first hour after infusion. Patients who suffered an AE were older than patients who did not ($p = 0.059$, in the limit of statistical significance). Patient sex and Volume and TNC of grafts were comparable between patients suffering or not an AE. Longer time of infusion was related to appearance of AE, in the limit of statistical significance ($p = 0.062$). Infusion of non-manipulated allogeneic grafts led to AEs in 23.0 % of patients, while infusion of washed grafts produced AEs in 39.2 % of patients, being this difference not statistically significant ($p = 0.114$). Within the allogeneic transplantations, 35 were ABO identical of which 26 had an AE, 12 were minor ABO incompatible of which 7 had an AE, and 13 were major ABO incompatible of which 12 had an AE ($p = 0.145$). Table 1 shows some characteristics of patients and grafts according to whether they developed or not an adverse event. More than one AE was reported in 26 patients (20.6%). Table 2 shows the characteristics of AEs. Hemolysis was not detected in any patient. Only one patient suffered a cardiovascular AE (hypertension). Twenty-eight patients (68.3 % of patients suffering any AE) received treatment to control the symptoms, being the most frequent administered drugs antipyretics + antiemetics. Two patients who suffered dyspnea after infusion required supplementary oxygen for a short period. All had a favorable outcome. None of the patient or graft characteristics included in the multivariable analysis showed statistical influence on AE appearance after HPC infusion.

Discussion

Adverse event rate after HSC infusion ranges from 8% to 90% in previous studies [12], those more frequently reported being skin rashes, nausea, vomiting, abdominal pain, chills and fever [6]. Infusion of thawed progenitor cells containing DMSO 10% has been related to an AE incidence of more than 20% [6,10,13]. DMSO is a cryoprotectant used for long-term storage of hematopoietic progenitor cells from bone marrow, peripheral blood and cord blood. It is well known that infusion of DMSO can cause a variety of AE including nausea, vomiting, flushing, fever, chills, cardiac symptoms, and rarely encephalopathy and seizures [14], without any impact on engraftment [15]. In order to reduce the DMSO content of

hematopoietic progenitor grafts, some cellular therapy laboratories perform manual or automatic washing of stem cell grafts. Lemarie et al. [16], Fois et al. [3], Sanchez-Salinas et al. [17] have reported an AE rate of less than 20% using an automated method for washing the progenitor grafts. Other authors [13] have reported similar results by performing manual washing of autologous stem cell grafts. Low rate of AE have also been reported in patients receiving washed cord blood grafts [18,19]. Our Transplantation Unit received the hematopoietic progenitor cells from both cord blood and peripheral blood thawed, washed and prepared for infusion from the Regional transfusion Centre. The adverse event rate of progenitor cell infusion in our patient population is 32.5%, significantly higher than in previous studies that also washed the grafts. It has to be focused that most AE were mild and all of them were well-controlled. Besides, cardiovascular AE were extremely rare, only 1 patient showed hypertension. Cardiovascular adverse events such as arrhythmias or hypertension occurred in 24% to 82% of patients receiving thawed but non-washed HPC products [20,21]. Since these complications are mainly related to DMSO, washing of HPC after thawing can be an effective strategy to reduce them. Results of our study and others show an important reduction of cardiovascular events when HPC washing is performed in routine [3,8,22]. Nevertheless, the DMSO reduction is not complete. Some authors have quantified the residual DMSO in washed progenitor cells using different washing protocols and they conclude they estimated the mean residual amount of DMSO as 0.8 ± 0.5 g [8]. According to our results, autologous infusions have higher adverse events rate without reaching this difference statistical significance, than allogeneic infusions of fresh and non-manipulated progenitor cells. Residual DMSO in HPC products may explain this difference. Donmez et al. [23] did not observe any infusion-related side effect in patients given allogeneic non-cryopreserved PBPC. On the contrary, in our study 23% of patients who received a non-cryopreserved graft presented some AE. It has to be noticed that most AE symptoms were mild and nonspecific. Recipients of HSC transplantation have different conditions that also can produce similar symptoms to AE after HPC infusion: they have received an intensive chemotherapy, are immuno suppressed and may have some infections. Apart of the DMSO, other graft characteristics have been related to the AE such as the amount of granulocytes [8], non-mononuclear cells [6], total nucleated cell content [5], and the presence of clumps [3]. Our study only has evaluated the volume and TNC content of grafts, concluding lack of influence of these factors on AE rate. Only longer time of infusion is associated with AE, without reaching this difference statistical significance. Regarding factors related to patient, age has been considered as a factor influencing AE in the study by Milone et al. [6]. Our study also shows a trend of older patients to suffer more AE. In our opinion, this has to be taken into account given the fact that an increasing number of autologous stem cell transplantations are performed in older patients. Gender and diagnosis of multiple myeloma has been previously considered as important factors for infusion-related toxicity [7], results not supported by our study. To our knowledge, this is the first study in which two different medications administered before infusion, have been compared. Use of medication is variable among centers, different combinations of diphenhydramine and steroids been usually employed. We have compared the patients who received steroids as part of premedication schedule or not. It has to be noticed that administration of steroids was associated to less AE, being this difference in the limit of statistical significance ($p = 0.090$). Patients who did not receive steroids were those who received thawed and

washed autografts containing residual DMSO. In our Transplantation Unit, graft infusion is performed directly from the bag by gravity. Mulay et al. [24] compared two different infusion techniques: manual push with syringes versus infusion from bags with the aid of gravity. The use of syringe infusion was more commonly associated with AEs, suggesting that the infusion from bags protect the patients from AEs. In summary, AEs after thawed/washed and non-cryopreserved HPC infusions occur in a significant number of patients, most of them being mild, non specific and well-controlled. Non cardiovascular events were extremely rare.

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