Clinical side effects during peripheral blood progenitor cell infusion

Ayhan Donmez *, Murat Tombuloglu, Ayse Gungor, Nur Soyer, Guray Saydam, Seckin Cagirgan

Ege University Medical School Hospital, Department of Internal Medicine, Division of Hematology, Bornova, 35100 Izmir, Turkey

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Abstract

There are several side effects which have been reported during the infusion of peripheral blood progenitor cells (PBPCs) either due to the infusion or the content of the infusate. We have evaluated the side effects detected during PBPCs infusion in 194 autologous and 25 allogeneic transplantations. In autologous cryopreserved PBPCs infusion, we detected a total of forty-nine (25.25%) side effect events during and after the infusion period. Forty-six (23.71%) of these side effects were detected during the infusion period including fifteen (7.73%) cardiac side effects, which required stopping the infusion, and thirty-one (15.97%) non-cardiac side effects, which did not require cessation of the infusion. Sinus bradycardia after a minimum of 45 min after completing the infusion was seen in three (1.54%) patients. The median volume, dimethyl sulfoxide (DMSO) and total nucleated cell (TNC) content of the product were found to be significantly higher in patients with side effects compared to the group without any side effects ($P < 0.05$). The median volume and DMSO content were found to be significantly higher in patients with cardiac side effects compared to non-cardiac side effects ($P < 0.05$). There was no cardiac side effects in patients treated with an infusate containing $10^9$ L$^{-1}$ leukocytes. We did not observe any infusion-related side effects in patients given allogeneic non-cryopreserved PBPCs. We have concluded that the volume, DMSO and TNC content of autologous cryopreserved PBPCs product are directly related to clinical side effects.

Keywords: PBPCs transplantation; Infusion; Side effects

1. Introduction

Intensive chemotherapy followed by hematopoietic progenitor cell (HPCs) transplantation has been used for several years in the treatment of certain hematological diseases. Progenitor cells from bone marrow (BM) have been replaced with peripheral blood progenitor cells (PBPCs) particularly over the last decades [1]. Infusion of HPCs is an important step in the transplant. Autologous PBPCs are classically frozen after leukapheresis collection by treating with dimethyl sulfoxide (DMSO) as a cryoprotective agent [1,2]. In allogeneic transplantation, the collected HPCs are transfused shortly after the collection [2].
In autologous transplantation, which is performed after 24–48 h of a conditioning regimen, the bags are usually thawed inside the patient’s room with a 37 °C water bath to shorten the exposure time of the HPCs to DMSO and then infused. Side effects are generally related to the infusate, and/or the infusion procedure. Infusion-related side effects could be caused due to volume [3], the content of DMSO [4,5] and red blood cell (RBC) [3,6] and the origin of the HPCs [6]. Additional factors originate from the patient such as previous treatment regimens which could increase the frequency and degree of side effects [7,8].

In allogeneic transplantation, the collected HPCs are, in general, not cryopreserved, no cryoprotectant is added, and they are usually kept at room temperature and/or refrigerated until they are infused in a short time [2]. The infusion of non-cryopreserved BM HPCs products has significantly fewer side effects compared to infusion of cryopreserved products [9,10].

In this study, we have presented the side effects detected clinically during and after infusion of autologous thawed cryopreserved PBPCs and allogeneic non-cryopreserved PBPCs in patients treated with high dose chemotherapy.

2. Patients and methods

We have evaluated the side effects detected during PBPCs infusion in our center between March 1998 and January 2006. We have performed 194 autologous and 25 allogeneic PBPC infusions between these dates. Eighty six of 219 patients were female and 133 were male with the median age of 42 (14–73). The patients’ characteristics based on groups are illustrated in Table 1.

2.1. PBPC mobilization and collection

Mobilization was performed by chemotherapy plus G-CSF in autologous patients and by only G-CSF in allogeneic donors. Apheresis in allogeneic donors was started at day 5. Patients for autologous transplantation were monitored daily by leukocyte counts and after the nadir, CD34+ cells were counted daily. Circulating CD34+ cell levels greater than 10 L\(^{-1}\) were accepted for the beginning of leukapheresis performed by using an automated apheresis system [COBE Spectra version 5.1 and version 6.0 (AutoPBSC), Cobe BCT Corp.; Fresenius ASTEC 204; Fenwal CS3000 plus, Baxter].

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>PBPCs transplantation</th>
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<tbody>
<tr>
<td></td>
<td>Autologous</td>
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<tr>
<td>No of patients</td>
<td>194</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>44 (14–73)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>115/79</td>
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<td>Diagnosis</td>
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</tr>
<tr>
<td>Primary amyloidosis</td>
<td>3</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
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</table>

2.2. PBPCs cryopreservation

Autologous cell products were diluted with autologous plasma to obtain a leukocyte count of 100 × 10\(^9\) L\(^{-1}\) in 151 patients and 200 × 10\(^9\) L\(^{-1}\) in 43 patients. At a different location, a mixture of 15% DMSO (Hybri-Max, Sigma), 6% HES (Expahes, Baxter) and 25% autologous plasma was prepared. The cell product and the cryopreservation mixture were gently mixed in the bags (Cryocyte Freezing container – 500 ml, Nexell) on ice. The products containing 7.5% DMSO, 3% HES and 12.5% autologous plasma in bags with a leukocyte count of 50 × 10\(^9\) L\(^{-1}\) (products of 151 patients) and 100 × 10\(^9\) L\(^{-1}\) (products of 43 patients) were placed in a –80 °C mechanical freezer after obtaining a last sample for microbiological culture.

Allogeneic PBPCs obtained on day 1 were kept in the refrigerator without any processing (no cryopreservation and without adding any cryoprotective agents) and day 0 products were handled without any waiting period by gentle shaking every 2 h until infusion.

2.3. High dose chemotherapy

High dose chemotherapy was initiated using BEAM in 77 patients (56 non-Hodgkin’s lymphoma, 21 Hodgkin’s lymphoma), melphalan in 69 patients (66 multiple myeloma and 3 primary amyloidosis), BU-CY in 65 patients (52 acute myeloid leukemia, 11 acute lymphoblastic leukemia, 2 paroxysmal nocturnal hemoglobinuria). Eight patients were treated with a reduced intensity conditioning regimen.
2.4. Infusion of PBPCs and patient monitoring

Twenty four to forty-eight hours after termination of the conditioning regimen, the cryopreservation bags were quickly thawed and re-infused to the patient. The refrigerated allogeneic products were infused to patients after keeping them at room temperature for 10–15 min. The infusion procedure was performed under close monitoring of a physician and two nurses as a standard procedure in our department. Patients were profilactically medicated with antiemetics, corticosteroids and antihistamines. Body temperature, blood pressure and heart rate were monitored closely before and during the infusion at 15 min intervals. The bags were thawed in the patient’s room using a 37°C water bath and infusion was immediately performed through a central venous line by using 200 μm standard transfusion filters that were commercially available without any automated pumps. Following infusion, body temperature, blood pressure and pulse were taken every 120 min over the following 6 h. This monitoring was sustained up to 24 h if needed in complicated patients.

Hypertension was defined as systolic >140 and diastolic blood pressure of >90 mm Hg.

2.5. Statistical analysis

All the data were analyzed with a statistical software package (GraphPad Prism version 4.03 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com). An unpaired T test was used to calculate the differences between groups. A one-way ANOVA test was used for comparison of more than two groups. P values less than 0.05 were considered significant.

3. Results

In a group of autologous cryopreserved PBPCs product, the median CD34+ positive cell count was 9.53 × 10⁶ kg⁻¹ (range 2.17–167), median TNC was 8.36 × 10⁸ kg⁻¹ (range 1.25–38.17) and the median volume of the product was 948.5 ml (range 75–5110). The infusion was performed with a median 11.88 ml/min (range 5–26.67) flow rate.

The median heart rate was found to be 88 min⁻¹ (range 60–120) pre-infusion and 88 min⁻¹ (range 60–124) at the end of the procedure. The median body temperatures were 36.5°C (range 34.6–38.5) and 36.6°C (range 35–38) at the beginning and after completing the procedure, respectively. There was no statistical difference in respect to heart rate and median body temperature pre-infusion and after infusion (P > 0.05).

Forty-nine (25.25%) side effect events were detected in the autologous group of which 46 were detected during the infusion period. Fifteen (7.73%) cardiac side effects (9 dyspnea, 3 hypertension, 2 lung edema, 1 left cardiac insufficiency) requiring cessation of the infusion were recorded during the infusion. Sinus bradycardia was detected in three (1.54%) patients of which one, occurring 45 min after completion of the infusion, was treated with atropine and another 2 at 180 min after finishing the infusion. Non-cardiac side effects (nausea and vomiting in 15, chills and tremor in 6, headache in 2, numbness in extremities in 2, stomach ache in 2, bad smell in 2, dizziness in 1, diarrhea in 1) were detected and treated without stopping the infusion in 31 (15.79%) patients (Table 2).

The median volume, median DMSO and median TNC content of the product were found to be significantly higher in patients with side effects compared to the group without any side effects (1200 ml vs. 910 ml, P = 0.03, 1.5 ml/kg vs. 0.92 ml/kg, P = 0.01 and 8.90 × 10⁸ kg⁻¹ vs. 7.83 × 10⁸ kg⁻¹, P = 0.004, respectively) while there were no differences in groups regarding the hematocrit and platelet count of the products and age (Table 3). Also, the median volume of the product and the median DMSO content of the product were found to be significantly higher in patients with cardiac side effects compared to non-cardiac side effects (2100 ml vs. 990 ml, P = 0.02 and 2.37 ml/kg vs. 1.26 ml/kg, P = 0.02, respectively) while there was no differences in groups regarding the hematocrit, platelet and TNC content of the products and age (Table 4).

There were a total of seven side effects without any cardiac events in patients treated with infusate containing 100 × 10⁹ L⁻¹ leukocytes. The median volume and DMSO content of the products were also statistically different in groups with 100 × 10⁹ L⁻¹ and 50 × 10⁹ L⁻¹ leukocyte (480 ml vs. 1233 ml, P < 0.0001 and 0.5 ml/kg vs. 1.33 ml/kg, P < 0.0001, respectively).

The median leukocyte count in products collected after 2003 was found to be significantly higher than the leukocyte count in products collected before 2003 (302 × 10⁹ L⁻¹ vs. 124 × 10⁹ L⁻¹, P < 0.0001). The median volume and DMSO content of the end products were found to be significantly lower compared to the products obtained before 2003 (500 ml
The median waiting periods at −80 °C for the products were not different between the groups whether they caused side effects or not (30 d vs. 29 d, \(P > 0.05\)).

In a group of allogeneic non-cryopreserved PBPC products, the median CD34 positive cell count was 5.66 \(\times\) 10^6 kg\(^{-1}\) (range 0.43–36.12), the median TNC was 8.18 \(\times\) 10^8 kg\(^{-1}\) (range 2.43–19.09) and the median volume of the product was 102.5 ml (range 30–330). The median heart rate was found to be 84 min\(^{-1}\) (range 64–96) pre-infusion and 80 min\(^{-1}\) (range 70–92) at the end of procedure. The median body temperatures were 36.6 °C (range 35.5–37) and 36.6 °C (range 36.4–36.8) at the beginning and after completing the procedure, respectively. There was no statistical difference in respect to heart rate and median body temperature comparing pre-infusion status and after infusion \((P > 0.05)\). We did not observe any infusion-related side effects in patients treated with allogeneic PBPCs infusion.

### 4. Discussion

Infusion of thawed HPCs (BM or PBPCs) has been associated with a wide variety of symptoms. Side effects are generally mild to moderate and
rarely life-threatening. The most frequent symptoms include nausea, vomiting, hypertension, hypotension and bradycardia. But headache, abdominal cramps, diarrhea, flushing, fever and chills have also been reported. The infusion of non-cryopreserved HPCs is generally better tolerated and has relatively fewer side effects [2].

Kessinger et al. reported the non-cardiac side effects in 100 autologous PBPCs transplanted patient with the ratio of 64–77% and they indicated that more RBC could cause more hypertension, chills, nausea, fever and more volume could result in more headaches [3]. We have observed non-cardiac complications with the ratio of 15.97%, which is less than Kessinger’s study. Although we have used infusion filters similar to this study, effective pre-medication could account for this outcome.

Alessandrino et al. have reported the ratio of non-cardiac complications as 8% and 57.33% for cardiac side effects in patients treated with PBPCs. They have found a positive correlation between high RBC content and cardiac toxicity after using BM products while there was no correlation in patients treated with PBPCs [6]. In our study, although we have fewer cardiac side effects (9.27%), non-cardiac side effects in our study were higher compared to this study. The absence of hypotension in our study is noted as the major difference. Although we could not document any relationship between RBC content of the product and side effects, the volume of the product and DMSO content had a direct relationship with side effects, especially cardiac side effects. The differences between our study and Alessandrino’s study could be attributed to the differences in the volume (988.5 in our study vs. 400 ml), differences in the DMSO content, which is relatively less in our study (7.5% vs. 10%) 3% concentration of HES, which was not used in above mentioned study.

Zambelli et al. have published the results of 22 autologous PBPC transplanted patients in respect to side effects. In their study, infusion-related side effects were reported in 50% of patients who were treated with the products stored with 10% DMSO (especially with use of more than 30 ml) in liquid nitrogen. The most prominent side effects were hypotension (22%), hypertension (4.54%), and bradycardia (4.5%) [4]. Davis et al. reported a lower degree of toxicity in recipients of density-gradient-separated grafts with a lower volume, including less DMSO, and fewer products of cell lysis than ofuffy-coat-separated grafts in 70 autologous BM transplanted patients [5]. We have used 7.5% DMSO in our PBPC products and kept them at −80 °C in a mechanical freezer. Our results support the outcome of these two studies, indicating that the DMSO content of the product is directly associated to the side effects.

The vast majority of cardiac side effects have been reported as self-limited and are not associated with serious morbidity and mortality. They have been detected during and up to several hours after the infusion [2]. Nevertheless, some serious complications such as bradycardia, requiring atropine treatment, have also been reported [4,6,11]. Two case reports describe a cardiac arrest immediately after the infusion of autologous BM [12,13]. Graves et al. reported 0.4% severe adverse reactions and 50% non-cardiac side effects in their study evaluating 1400 infusion procedures which included PBPCs and BM products processed with 10% DMSO [14]. In our study, we have detected three (1.54%) serious events (pulmonary edema in 2 patients and left heart insufficiency in 1 patient) which required stopping the infusion and the patient completely recovered after immediate interventions. Additionally, we observed three events (1.54%) of sinus bradycardia, one of them at 15 min into the infusion and the others at 180 min from which the patients recovered after atropine injections. Of these 3 patients, one with sinus bradycardia with a body temperature of 35.1 °C causing limited systemic hypothermia symptoms, while the others had 36.2 and 36.6 °C body temperatures without any sign of systemic hypothermia.

Keung et al. reported the cardiac side effects as the result of infusion of products with a content of 5% DMSO, 6% HES, BM or PBPCs. They reported 65% sinus bradycardia, 29.41% with heart block and 41% hypertension in 17 patients, retrospectively [8]. In contrast to this study, Lopez-Jimenez et al. published the prospective results of 6 PBPCs and 29 autologous BMT (with 10% DMSO) procedures monitored by Holter method. They reported 41% of non-cardiac side effects and no bradycardia and arrhythmias [9]. We did not detect any arrhythmias in the clinical presentation in our patients treated with autologous PBPCs processed with 7.5% DMSO and 3% HES, compared to the first study. Also, we detected a lower number of non-cardiac side effects than in the second study and no arrhythmia during infusion similar to this study.

The infused TNC in the group with side effects was found to be significantly higher than in the
group with no side effects ($P = 0.004$). Regarding the groups with cardiac and non-cardiac side effects, comparison of the amount of TNC between groups with and without side effects showed that statistical significance disappeared in the group with cardiac side effects, however, it continued in the group with non-cardiac side effects ($P = 0.001$). Our results revealed that the amount of infused TNC could be a factor contributing to the side effects.

We have been using several different leukapheresis devices in our center since 1998. Improvements in the technological aspects during these years have provided greater numbers of leukocytes in the products with lower volume. Hence, comparison of the products collected before and after 2003 showed that the products obtained after 2003 have a greater amount of leukocytes and a lower volume and DMSO content. As a result of this situation, the vast majority of side effects (11 of 15 cardiac side effects) including life-threatening events such as 2 pulmonary edemas and 1 left heart insufficiency were detected before 2003. Cardiac side effects seen after 2003 were easily minimized by using some interventions such as decreasing the infusion rate, pausing for short periods and administering diuretics. Also, using the fractionated infusion as reported by Martin et al. [11], early use of diuretics, infusion of the product with a volume of over 1500 ml in two sessions could be evaluated as additional positive factors to decrease cardiac side effects.

We cryopreserved the collected products by diluting them so that the final leukocyte count was $50 \times 10^9$ L$^{-1}$ until the last 2 yr. For the last 2 yr, we have been using a final leukocyte count of $100 \times 10^9$ L$^{-1}$ for most of the collected products. The products with a final leukocyte count of $100 \times 10^9$ L$^{-1}$ were found to have significantly lower volumes and DMSO content compared to other products. This provided at least a 50% decrease in the infusion duration. We detected no cardiac side effects and less non-cardiac side effects in patients treated with the products containing $100 \times 10^9$ L$^{-1}$ leukocytes, lower volume and lower amount of DMSO.

Our experiences showed that the best way to decrease the occurrence of side effects during autologous PBPCs infusion was to obtain products with a higher content of mononuclear cells and the lowest volume possible. Especially, using products with a final leukocyte count of $100 \times 10^9$ L$^{-1}$ would prevent the cardiac side effects and minimize the non-cardiac side effects. Also, effective pre-medication (antiemetics, corticosteroids and antihistamines) and using standard transfusion sets would be other contributing factors to decrease the infusion-related side effects. It could be recommended that a fractionated infusion procedure be performed with 2 h intervals, and diuretics be administered early in patients treated with high volume products.

In allogeneic BM or PBPC transplantation, the collected HPCs are transfused shortly after collection. They are, in general, not cryopreserved, no cryoprotectant is added, and they are usually kept at room temperature until they are infused. The infusion of a non-cryopreserved product is generally better tolerated [2]. Lopez-Jimenez et al. [9] and Stroncek et al. [10] patients transfused with cryopreserved marrow had significantly more non-cardiac side effects than patients transfused with fresh allogeneic marrow. We did not observe any clinical side effects during the infusion of fresh allogeneic PBPCs products.

As a result of this study, we can recommend use of autologous PBPCs products with a relatively high final leukocyte count with less volume and lower amounts of DMSO to decrease the infusion-related side effects.

References


