Comparative assessment of prophylactic transfusions of platelet concentrates obtained by the PRP or buffy-coat methods, in patients undergoing allogeneic hematopoietic stem cell transplantation

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Abstract

Objectives: Whole blood-derived platelet concentrates can be obtained by the platelet-rich plasma (PRP-PCs) or the buffy-coat (BC-PCs) method. Few studies have shown that BC-PCs display lower in vitro platelet activation, but scarce information exists regarding transfusion efficacy. We have performed a retrospective study assessing platelet transfusion in patients undergoing allogeneic hematopoietic cell transplantation (AHCT) in our clinic, before and after the implementation of BC-PCs.

Methods: We reviewed clinical records corresponding to 70 PRP-PCs and 86 BC-PCs prophylactic transfusions, which were performed to 55 AHCT patients. Transfusion efficacy was assessed by the 24-h post-transfusion corrected count increment (24-h CCI) and bleeding events. Clinical factors affecting transfusion outcome were also investigated.

Results: Clinical characteristics and the total number of platelet transfusions were similar among groups. Mean donor exposure was 5.8 and 5.0 in each single PRP-PCs and BC-PCs transfusion, respectively (p < 0.01). The 24-h CCI was significantly higher in patients transfused with BC-PCs than in those receiving PRP-PCs (8.3 [2.7–13.4] vs. 4.7 [1.3–8.1]; p < 0.01). Independent predictors of poor platelet transfusion response included diagnosis other than acute leukemia (HR 8.30; 95% CI 1.96–35.22; p = 0.004), splenomegaly (HR 8.75; 95% CI 2.77–27.60; p < 0.001), graft versus host disease prophylaxis different from cyclosporine A and methotrexate (HR 3.96; 95% CI 1.55–10.14; p = 0.004) and PRP-PCs transfusion (HR 4.54; 95% CI 1.72–12.01; p = 0.002). There were no differences between both groups regarding the bleeding events.

Conclusion: In the AHCT setting, we hypothesize that BC-PCs transfusion, when compared to PRP-PCs, results in higher CCI and reduced donor exposure, but provides no significant benefit regarding bleeding outcome.

Introduction

Patients undergoing allogeneic hematopoietic cell transplants (AHCT) experience a high risk of bleeding complications secondary to the chemotherapy-induced thrombocytopenia. Although the correct transfusion practice after AHCT is still controversial [1], most platelet transfusions in this clinical setting are prophylactic, aiming to increase the low platelet counts and to reduce the risk of bleeding. The Platelet Dose Study (PLADO) has shown that low-dose prophylactic platelet transfusions could reduce total platelet utilization without increasing the risk of grade ≥2 bleeding [2]. In contrast, the Trial of Prophylactic Platelet Transfusions (TOPPS) has suggested that a strategy of therapeutic platelet transfusion, i.e. transfusion only in case of bleeding, might become a new standard of care in selected patients [3].

While those issues, low vs. high dose or prophylactic vs. therapeutic platelet transfusion, are currently under debate and investigation, little is known regarding the impact of the type of platelets being transfused in this clinical setting. Nowadays, the respective use of PCs and apheresis platelets (AF-PCs) is highly heterogeneous, ranging from 10% to 98% PCs [4]. Whereas the Netherlands or Sweden uses buffy-coat derived platelet concentrates (BC-PCs) as standard platelet product for patient care, the UK or France applies AF-PCs [5]. To our knowledge, randomized clinical trials evaluating platelet transfusion outcomes have included mainly apheresis platelets, whereas studies
evaluating whole-blood-derived platelets (WBDP) products are scarce [2,3].

It is long known that platelets undergo various changes from blood collection, and during processing and blood banking storage, collectively referred to as platelet storage lesion (PSL) [6]. These ex vivo changes in platelets, as well as the patient’s clinical conditions, may affect the therapeutic benefit of platelet transfusion [7–9]. In the 1990s an in vitro study showed that BC-PCs undergo less PSL than PRP-PCs [10]. Metcalfe et al. also found that processing-induced platelet activation was lower in BC-PCs than in PRP-PCs [11]. So far, few comparative studies have shown negligible differences in transfusion efficacy between these two platelet products [12–14]. Regarding safety issues, PRP-PCs have displayed a higher bacterial contamination risk, compared to BC or AF-PCs [15].

In the current investigation, we have retrospectively compared the outcome of prophylactic platelet transfusions with either BC-PCs or PRP-PCs in a series of patients undergoing AHCT.

Materials and methods

Patients

A series of 55 consecutive patients underwent AHCT in our Hematology Unit at the Morales Meseguer University Hospital, between January 2005 and February 2011. Until February 2008, patients were transfused, if required, with PRP-PCs or single-donor apheresis platelets (AF-PCs). Then, PRP-PCs production was discontinued by the local blood transfusion center. From March 2008, AHCT patients received, if needed, AF-PCs or BC-PCs.

This investigation followed the principles of the Helsinki Declaration and had been approved by the hospital Ethics Committee. Patients had provided consent for using their medical records for research purposes.

For the aim of the study, these patients were classified into two groups according to the type of prophylactic WBDP product being transfused, i.e. PRP-PCs and BC-PCs. Patients in both groups could also receive AF-PCs during post-AHCT clinical management, depending on the availability of platelet products in the blood transfusion center. In these series of AHCT patients, platelet engraftment was defined as the first of three consecutive days with a platelet count \(>20 \times 10^9/L\) without transfusion, or the second day of three days with a platelet count higher than \(20 \times 10^9/L\) after a platelet transfusion. Neutrophil engraftment was considered as the first day of three consecutive days with an absolute count \(>0.5 \times 10^9/L\). According to the criteria established in our Clinical Unit, prophylactic platelet support was given to patients with platelet counts in the daily morning count of less than \(10 \times 10^9/L\), or less than \(20 \times 10^9/L\) under particular clinical conditions, such as fever or sepsis, at the physician decision.

Platelet transfusions in these patients were not considered in the study according to the following exclusion criteria: therapeutic transfusion in the context of grade \(\geq 2\) bleeding according to the World Health Organization (WHO scale); prophylactic transfusion given with a threshold higher than \(20 \times 10^9/L\); multiple platelet transfusions on the same day; transfusion in the presence of thrombotic thrombocytopenic purpura or the hemolytic–uremic syndrome.

Patient bleeding complications following AHCT were assessed by reviewing medical daily records. Bleeding diathesis in patients was graded by two independent investigators, and a third in case of discrepancy, according to the WHO bleeding Scale as used in the PLADO trial [2].

Platelet concentrates preparation

Whole blood samples (450 ± 50 mL) from regular blood donors were collected into licensed triple bag systems (Terumo BCT, Zaventem, Belgium; Laboratorios Grifols SA, Barcelona, Spain), with a primary pack containing 63 mL of CPD anticoagulant.

WBDP individual units were obtained by PRP method as described [16], and stored under standard blood bank conditions (20–24°C, 60 cycles/min) for up to five days. PRP-PCs transfusion units were prepared immediately before transfusion by pooling of individual ABO-identical PRP-platelet units based on the patient’s weight. All PRP-PCs were leukodepleted by filtration at bedside at time of transfusion.

Leukodepleted BC-PCs transfusion units, in plasma (35%) and platelet additive solution (65%) (SSP+, Macopharma-MacoSpaina, Madrid, Spain) were obtained from whole blood units by the BC procedure, as detailed elsewhere [17]. BC-PCs were stored as above until transfusion within five days from preparation.

Leukodepleted AF-PCs transfusion units were obtained directly from donors using TRIMA or COBE Spectra apheresis devices (Terumo BCT) according to the manufacturer’s instructions. Our standard apheresis procedure did not change during the study period (January 2005 to February 2011).

The general characteristics of the patients as well as the properties of the platelet transfusion units which may affect platelet transfusion were recorded at patient the medical history and the Blood Center database, respectively, and are summarized in Tables 1 and 1S.

Platelets transfusion assessment

The primary endpoints of the study were post-transfusion platelet increment (PPI) and correct count increment (CCI), as previously defined [18]. The platelet
number in the transfused units was not available. Therefore, we used the mean platelet number reported by the blood transfusion center in the quality assessment of PCs performed at the corresponding time. The 24-h CCI cutoff for platelet refractoriness was set at 4500 [13]. Secondary outcomes included the percentage of patients who had bleeding events of WHO grade \( \geq 2 \), death from hemorrhage, total number of platelet transfusions, prophylactic transfusion intervals and time from the first transfusion to bleeding grade \( \geq 2 \). Patients’ follow up concluded when they achieved platelet engraftment (\( \geq 20 \times 10^9/L \)) at hospital discharge or at death, whichever occurred first.

**Statistical analysis**

Given the retrospective and observational design of this study, we have not performed any sample size calculation. Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Categorical variables are presented as a percentage and continuous variables as median (interquartile range). Chi-square or Fisher’s exact test for qualitative variables and T-student or U test and correlation analyses for quantitative were performed, as appropriate, to evaluate differences in patient’s characteristics and to check for the potential effect of patient and/or PCs characteristics on 24-h CCI. The independent effect of clinical variables on the platelet transfusion response was calculated using a Cox proportional hazards regression model, incorporating in the multivariate model only those variables that showed a \( p \) value <0.15 in the univariate analysis. Statistical significance was established at \( p \) values <0.05. All statistical analysis was performed using SPSS version 15.0 for Windows software.

**Results**

**Patient general characteristics**

During the study period, 330 platelet transfusions were performed to 74 patients who underwent AHCT. Among these, 123 were excluded as they were therapeutic transfusions. Fifty-one prophylactic AF-PCs transfusions were evaluated separately (see Table 2S). The remaining 156 analyzed transfusions corresponded to 70 PRP-PCs transfusions to 27 patients, and 86 BC-PCs units that were transfused to 28 patients.

The general clinical conditions of these 55 patients as well as their transplant characteristics are summarized in Table 15. As shown, no statistically significant differences between both groups were observed regarding patient characteristics, underlying disease, or the transplant peculiarities. Both groups behaved similarly in terms of neutrophil and platelet engraftment (Table 15). All patients received hepatic sinusoidal obstructive syndrome prophylaxis with low molecular weight heparin, and none of them developed clinical signs of this complication. The number of sepsis episodes was similar in both groups. Concomitant treatment with amphotericin B and platelet transfusion did not take place in the PRP-PCs group, but occurred in 12% of the cases in the BC-PCs group. Remarkably, red blood cell transfusions (RBCT) were significantly less frequent in the PRP-PCs group than in the BC-PCs group (median 4 vs. 6, \( p = 0.025 \)).

**Platelet concentrates properties and platelet transfusion efficacy**

The estimated platelet contents of the PRP-PCs before bedside filtration, and leukodepleted BC-PCs transfused to the patients were 3.90 ± 0.47 and 3.85 ± 0.18 × 10^{11}, respectively (\( p = 0.33 \)). BC-PCs were stored before transfusion for slightly shorter times than PRP-PCs (3.49 ± 1.13 days vs. 3.93 ± 1.01 days, \( p < 0.02 \)). In addition, the mean number of donors involved in each platelet transfusion unit was significantly lower in BC-PCs when compared to the PRP-PCs (5.01 ± 0.19 vs. 5.76 ± 0.53 donors, respectively; \( p < 0.01 \)).

Regarding the AF-PCs transfused to patients, no major changes took place in their collection and processing during the study period. These leukocyte depleted AF-PC averaged 3.39 ± 1.16 × 10^{11} platelets per unit. Moreover, the mean storage time of AF-PCs before transfusion was similar in patients from the PRP-PCs and the BC-PCs groups (3.65 ± 1.27 days vs. 3.03 ± 1.17 days, respectively; \( p = 0.08 \)).

Overall, patients in either group received a median of three platelet transfusions during the engraftment period. Importantly, there were no statistical differences in the proportion of AF-PCs and whole blood-derived PCs that were transfused to either group of patients (see Table 1).

**Table 1.** Total platelet transfusion and efficacy of WBDP transfusions in both patient groups.

| Parameter                              | PRP-PCs \( n = 27 \) | BC-PCs \( n = 28 \) | \( p \) Value |
|----------------------------------------|----------------------|---------------------|--------------|
| Total platelet transfusions            | 90                   | 117                 |              |
| Platelet type                          |                      |                     |              |
| WBDP                                   | 70 (78)              | 86 (73.5)           | 0.27         |
| Apheresis                              | 20 (22)              | 31 (26.5)           |              |
| Platelet transfusion per patient       | 2 (2–4)              | 3 (1.3–6.8)         | 0.44         |
| WBDP transfusion efficacy assessment   |                      |                     |              |
| Pre-transfusion platelet count (\( \times 10^9/L \)) | 13 (11–16)          | 14 (11–17)          | 0.35         |
| 24-h Post-transfusion platelet count (\( \times 10^9/L \)) | 22.5 (16.8–32)     | 31.5 (21–42)        | 0.024*       |
| 24-h platelets increment (\( \times 10^9/L \)) | 9 (3–19)            | 18 (7–26.3)         | 0.032        |
| 24-h CCI (\( \times 10^9/L \))        | 4.75 (1.2–8.4)       | 8.7 (3–13.5)        | <0.01*       |
| >4.5 × 10^9/L 24-h CCI – % of transfusion | 37 (53)             | 60 (70)             | <0.05*       |
| Days until next transfusion            | 1.9 (1–3)            | 2 (1.5–3)           | 0.6          |

Note: All values are shown as median and interquartile range or absolute number and percentage.

\( *p < 0.05 \) with respect to PRP-PCs group.
As summarized in Table 1, both PPI and CCI were approximately 2-fold higher in the BC-PCs than in PRP-PCs transfusion group. Moreover, the percentage of inefficient platelet transfusions, i.e. 24-h CCI < 4500, was significantly lower in patients receiving BC-PCs. In contrast, we found no significant differences between the two groups in the efficacy of apheresis platelet transfusion (Table 2S). We observed a similar time to next transfusion in both groups (Table 1).

Univariate analysis revealed that factors statistically associated with lower 24-h CCI included female gender, age older than 43-year-old, PRP-PCs transfusion and several clinical variables (Table 2). In contrast, in this series of transfusions, hepatomegaly, ABO compatibility, PCs storage time and patient body surface area had negligible effect in CCI-24-h (data not shown). In the Cox regression multivariate analysis, variables that remained independently associated with poor platelet transfusion response included diagnosis different from acute leukemia (AL) (HR 8.30; 95% CI 1.96–35.22; p = 0.004), splenomegaly (HR 8.75; 95% CI 2.77–27.60; p < 0.001), GvHD prophylaxis different from CsA and MTX (HR 3.96; 95% CI 1.55–10.14; p = 0.004) and PRP-PCs transfusion (HR 4.54; 95% CI 1.72–12.01; p = 0.002; Table 2).

On secondary analysis, we evaluated the influence of the type of PCs on patient bleeding and transfusion interval. Here, 25 patients corresponding to PRP-PCs group and 27 to BC-PCs were available for analysis. As shown in Table 3, bleeding grade ≥2 occurred in 23% of the patients, with slightly higher incidence among those of the PRP-PCs group (832%) [5 bleeding grade 2 and 3 grade 3] vs. 415% [3 bleeding grade 2 and 1 grade 4] in the BC-PCs group). Gastrointestinal bleeding was the most common bleeding complication among PRP-PCs patients (62.5% of the patients), followed by urinary, gynecological and cutaneous bleeding (12.5% each). In contrast, epistaxis was the most frequent bleeding in the BC-PCs group (50%), followed by gastrointestinal and urinary bleeding (25% each). Overall, cutaneous bleeding was the most common mild bleeding event (64% of bleeding grade 1), without differences between PRP-PCs and BC-PCs groups. One patient in the BC-PCs displayed refractoriness to multiple transfusions and died from generalized bleeding (intracranial, hematuria, pulmonary hemorrhage, etc.), before a specific HLA/HPA typed apheresis platelet transfusion protocol could be established.

Finally, the time interval from the first transfusion to first bleeding grade ≥2 episode, was similar in both patient groups (Table 3).

Table 2. Factors associated with a poor response, i.e. lower 24 CCI, to platelet transfusion.

| Characteristics                  | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | HR (95% CI); p       | HR (95% CI); p         |
| Patient related                  |                     |                       |
| Female gender                    | 3.78 (1.91–7.49); p = 0.001 | 1.90 (0.68–5.23); p = 0.216 |
| Age ≥ 43 years                   | 1.03 (1.01–1.06); p = 0.003 | 1.03 (0.99–1.06); p = 0.143 |
| Splenomegaly                     | 4.32 (1.90–9.84); p < 0.001 | 8.75 (2.77–27.60); p < 0.001* |
| Diagnosis different from AL      | 13.67 (4.00–46.73); p < 0.001 | 8.30 (1.96–35.22); p = 0.004* |
| BM stem cells source             | 2.91 (1.24–6.81); p = 0.014 | 1.45 (0.40–5.41); p = 0.577 |
| Reduced intensity conditioning regimen | 5.21 (2.37–11.46); p < 0.001 | 2.15 (0.62–7.50); p = 0.230 |
| Prophylaxis different from CsA-MTX | 2.64 (1.34–5.20); p = 0.005 | 3.96 (1.55–10.14); p = 0.004* |
| Mucositis grade ≤2               | 2.21 (0.92–5.30); p = 0.075 | 2.63 (0.68–10.27); p = 0.163 |
| Product related                  |                     |                       |
| PRP-PCs transfusion              | 2.06 (1.07–3.97); p = 0.031 | 4.54 (1.72–12.01); p = 0.002* |

Note: HR = hazard ratio; CI = confidence interval.
*p < 0.05 with respect to PRP-PCs group.

Table 3. Bleeding complications in both patient groups.

| Characteristics                  | PRP-PCs | BC-PCs | p Value |
|----------------------------------|---------|--------|---------|
| Number of patients               | 25      | 27     | 0.14    |
| Bleeding during the study        |         |        |         |
| Grades 0–1                       | 17 (68) | 23 (85) |         |
| Grade ≥2                         | 8 (32)  | 4 (15) |         |
| Days from platelet transfusion to first bleeding grade ≥2 | 5.6 (3.6–8.1) | 6.7 (2.5–12.5) | 0.60 |
| Deaths from hemorrhage            | 0       | 1      |         |

Note: All values are shown as median and interquartile range or absolute number and percentage.

Discussion

Although the preparation of WBDP by the BC method has widely substituted the PRP procedure worldwide, to date few studies have compared transfusion outcome of BC-PCs and PRP-PCs [13,14,19]. Prospective studies approaching this comparison will unlikely to be made nowadays, since the production of PRP-PCs has already been abandoned in most developed countries.

Previously, Anderson et al., ‘in the pre universal leukoreduction era’, have reported that the use BC-PCs, vs. PRP-PCs, was associated with slightly, but not significantly, higher CCI values, as well as with lower non-hemolytic febrile transfusion reactions [19]. More recently, Singh et al. have compared transfusion outcomes of single-donor apheresis, BC and PRP platelets, and reported comparable CCI and percentage of platelet recovery with either product. Potential bias in that study was patient heterogeneity and unclear separation among prophylactic or therapeutic platelet transfusions [14].

A major finding in our retrospective study is a significantly higher percentage of efficacious transfusions (i.e.
in 24-h CCI > 4500) for BC-PCs than for PRP-PCs transfusions (70% vs. 53%), and this result was corroborated in the multivariate analysis. As our transfusion policy and transplant management were not significantly modified within the study time, these features could have had negligible influence on transfusion efficacy. Moreover, the transfusion benefit associated with BC-PCs is unlikely to be due to major differences in patient characteristics over time (2005–2007 vs. 2008–2011), as the efficacy of AF-PCs transfusions was similar in BC-PCs and PRP-PCs patient groups.

Other variables identified in the multivariate analysis as independently associated with higher transfusion efficacy were the absence of splenomegaly, GvHD prophylaxis with CsA-MTX and diagnosis of AL.

These findings are in agreement with previous studies showing that splenomegaly reduces PPI in oncohematology patients [8,20]. It has also been shown that GvHD prophylaxis may influence transfusion efficacy. Thus, Besinguer et al. have reported that patients receiving MTX alone for GvHD prophylaxis require significantly more units of platelets than those receiving CsA or CsA-MTX combination [21]. In addition, Ishida et al. showed that high serum levels of tacrolimus or CsA strongly associate with a poor transfusional response [22]. In contrast to our finding, a previous study has reported negligible influence of AL diagnosis in CCI, but this investigation was not restricted to prophylactic transfusions as herein [20].

In the last two decades, bleeding outcomes have become the primary endpoint of platelet transfusion studies. In line with results published by Rebulla [23], the most common bleeding event in our study was mild skin bleeding, although the most frequent grade ≥2 bleeding complication was gastrointestinal bleeding. Overall, we observed a low rate of bleeding (15–32%) in our study. Of mention, a high variability in bleeding rate (10–70%) has been reported in the different clinical trials [2,3,23] which may be explained by the way the investigators have recognized and graded bleeding events [24]. While, as stated above, transfusion of BC-PCs favors higher platelet count increment, it is remarkable that this variable showed no apparent influence in patient bleeding outcomes. Similarly, secondary analyses of PLADO study demonstrated that transfusing apheresis platelets, ABO-identical platelets or platelet stored ≤3 days benefit platelet count increment, but these variables had no significant effect in time to bleeding events’ grade ≥2 [9].

An unexpected finding was a higher number of RBCT in BC-PCs, despite these patients showed less bleeding complications. A sub-analysis of the patients in the TOPPs study who underwent chemotherapy or AHCT showed that patients receiving prophylactic platelet transfusions had significantly lower number of bleeding complications than those in the no-prophylaxis arm. However, this finding did not associate with significantly lower number of RBCT [25]. These results suggest that multiple variables are involved in RBCT requirement in the ASCT setting [26]. Further studies, beyond the scope of this investigation, are needed to assess the role of platelet transfusion in the complex relationship of RBCT and bleeding.

An additional benefit observed in this study was the reduction in donor exposure with each BC-PCs transfusion (five donors vs. six in the PRP-PCs group) during the engraftment period. This small, but significant, reduction may provide additional protection to patients toward pathogen infection and potentially towards allo-immunization. A real estimation of such potential benefit would require a randomized clinical trial that would be troublesome to perform nowadays. Of mention, the TRAP study showed no difference in allo-immunization rate between leukoreduced single-donor (i.e. apheresis) platelets and leukoreduced pooled random-donor platelet concentrates [8]. Later, a meta-analysis of studies comparing transfusion of different WBDP drew no conclusions regarding allo-immunization and refractoriness outcomes [13].

We ought to recognize some limitations in this study. First, it is a retrospective study and data analysis is based on the review of medical records. Second, most patients in both BC-PCs and PRP-PCs groups received AF-PCs sporadically, if transfusion was required and WBDP were not available. Yet, the number of AF-PC transfusions in both groups was similar. Third, although our transfusion criteria and patient management are thought to be similar along the full study period (2005–2011), some variables such as the Amphotericin B administration was found to be higher in BC-PCs transfusion period. The use of this drug has been described to have a negative effect on CCI [27], which could by no means be discarded in our study. Yet, in our study, Amphotericin B administration was present in only 12% of the BC-PCs transfusions, and this platelet product was associated with higher platelet increments than PRP-PCs. Finally, the uncertainty that transfusion reactions were systematically reported in clinical records prevented us from comparative analysis of such events in the two patient groups.

**Conclusions**

In summary, this retrospective study shows that transfusion of BC-PCs, in comparison with PRP-PCs transfusion, favors superior post-transfusion platelet count increments and reduced mildly, but significantly, donor exposure for WBDP transfusion episodes. However, BC-PCs is equivalent to using PRP-PCs in terms of prevention of major bleeding complications in AHCT patients. We further confirm that patient clinical conditions such as the type of disease, splenomegaly and GvHD prophylaxis management, play an
important role in transfusion outcome and should be considered in estimating the patient bleeding risk, irrespective of the platelet product transfused. Identification of increased bleeding conditions may change our transfusion practice from room-temperature-stored platelets towards other type of platelets, e.g. refrigerated platelets, which may be more beneficial in patients with high bleeding risk.

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