Platelet transfusion refractoriness after T-cell-replete haploidentical transplantation is associated with inferior clinical outcomes

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Haploidentical stem cell transplantation (haplo-SCT) has been an alternative source of bone marrow for patients without human leukocyte antigen (HLA)-matched donors. The aim of this study was to investigate the relationships between platelet transfusion refractoriness (PTR) and clinical outcomes in the setting of haplo-SCT. Between May 2012 and March 2014, 345 patients who underwent unmanipulated haplo-SCT were retrospectively enrolled. PTR occurred in 20.6% of all patients. Patients in the PTR group experienced higher transplant-related mortality (TRM, 43.7% vs. 13.5%, \(P<0.001\)), lower overall survival (OS, 47.9% vs. 76.3%, \(P<0.001\)) and lower leukemia-free survival (LFS, 47.9% vs. 72.3%, \(P<0.001\)) compared to patients in the non-PTR group. The multivariate analysis showed that PTR was associated with TRM (\(P=0.002\)), LFS (\(P<0.001\)), and OS (\(P<0.001\)). The cumulative incidences of PTR in patients receiving >12 platelet (PLT) transfusions (third quartile of PLT transfusions) were higher than in patients receiving either >6 (second quartile) or >3 (first quartile) PLT transfusions (56.1% vs. 41.6% vs. 28.2%, respectively; \(P<0.001\)). The multivariate analysis also showed that PTR was associated with the number of PLT transfusions (\(P<0.001\)). PTR could predict poor transplant outcomes in patients who underwent haploidentical SCT.

Platelet transfusion refractoriness, unmanipulated haploidentical stem cell transplantation, clinical outcomes, PLT transfusion

INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment for patients with hematological malignancies (Aversa et al., 2005; Baron et al., 2015; Chang and Huang, 2012; Chang and Huang, 2016; Reisner et al., 2011; Wang et al., 2014a; Wang et al., 2014b; Zhao et al., 2016). Thrombocytopenia (especially persistent thrombocytopenia) is common after allo-SCT and is associated with potential morbidity and mortality (Dominietto et al., 2001). Therefore, platelet (PLT) transfusion is a key supportive therapy for patients undergoing allo-SCT. However, PLT transfusions are not effective enough to increase PLT counts in patients who experience platelet transfusion refractoriness (PTR), which is defined as the repeated failure to obtain satisfactory responses to PLT transfusions. Previous studies showed that an increasing number of PLT transfusions was significantly associated with an increased risk of experiencing PTR in the setting of patients with acute myeloid leukemia (AML) who received induction chemotherapy (Slichter et al., 2005) and patients who underwent autologous SCT for AML (Toor et al., 2000). Despite the PTR, PLT transfusion remains an important sup-

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portive therapy for patients undergoing allo-SCT.

Recent studies about PTR mainly focused on the causes and the solutions (Forest and Hod, 2016; Hod and Schwartz, 2008; Tagariello et al., 2016). Studies of the relationship between PTR and clinical outcomes are rare. Kerkhoffs et al. showed that the patients who did not experience 24-hour transfusion failure had superior 100-day survival ($P<0.01$) and median survival ($P=0.032$) rates compared to patients experiencing one or more episodes of transfusion failure among a cohort of 110 patients who received cytotoxic therapies including chemotherapy, allo-SCT, and autologous SCT (Kerkhoffs et al., 2008). In patients with AML who underwent autologous stem cell transplantation, the median leukemia-free survival of PTR patients in leukemia-free was 5 months if they experienced PTR compared to 26 months in patients without PTR (Toor et al., 2000).

Recently, increasing numbers of studies have focused on allo-SCT, especially haploidentical SCT (haplo-SCT) (Lv and Huang, 2015). Haploidentical patients suffer from delayed PLT engraftment compared to patients receiving SCT from matched donors (Wang et al., 2015); therefore, these patients would receive more PLT transfusions. However, there are no studies concerning the relationship between PTR and the number of PLT transfusions in the setting of haploidentical HSCT. In addition, the relationships between PTR and overall survival (OS), LFS, acute graft-versus-host disease (aGVHD), transplant-related mortality (TRM) and relapse remain unclear in the setting of haplo-SCT. Therefore, in the present study, we analyzed the effects of PTR on clinical outcomes and the association between PTR and PLT transfusions in the setting of haploidentical HSCT.

RESULTS

Patient characteristics and clinical outcomes

A total of 345 patients were included in the analysis and divided into two groups according to PTR. Patients who experienced PTR between days +1 to +100 after allo-SCT were stratified in the PTR group, and all other patients were in the non-PTR group. The median age was 26 years. All patients were treated with a myeloablative conditioning regimen. The demographics are listed in Table 1. Most of the patients’ characteristics between the two groups were similar except for age and gender matching. The PTR group had an older median age (31 years) and a higher percentage of female-male gender matching (31%). The final follow-up was April 1, 2016. Of the cohort, 342 patients (99.1%) achieved myeloid engraftment at a median time of 13 days (range, 8–27 days). Approximately 92.5% of all patients (319 patients) achieved PLT engraftment with a median time to PLT engraftment of 17 days (range, 6–265 days). The incidence of primary GF was 6.1% (21 patients). During the entire follow-up, 44 patients (12.8%) experienced relapse, and 19.7% of the patients died of TRM. The percentages of OS and LFS were 70.4% and 67.2%, respectively. At 100 days post-transplantation, the percentage of patients who experienced aGVHD (grade II–IV) was 34.2% (Table 2).

Association between PTR and clinical outcomes after transplantation

Acute GVHD

The cumulative incidences of acute GVHD (grade II–IV) in the PTR and non-PTR groups were 33.8% and 34.3%, respectively ($P=0.874$) (Table 2). The univariate analysis showed that the age of the recipient, the donor-recipient relationship and PLT transfusion were associated with acute GVHD (grade II–IV) (Table S1 in Supporting Information). The multivariate analysis showed that older recipients and more PLT transfusions were associated with acute GVHD (grade II–IV) (Table 3, Figure 1).

Relapse

There were no significant differences in the percentage of patients who relapsed between the PTR and non-PTR groups (9.9% vs. 13.5%, $P=0.971$) (Table 2, Figure 2A). Only disease status was associated with relapse in both the univariate analysis and multivariate analysis.

TRM

The incidence of TRM was higher in the PTR group than in the non-PTR group (43.7% vs. 13.5%, $P<0.001$) (Table 2, Figure 2B). The univariate analysis showed that the variables affecting TRM included the age of the recipient, ABO compatibility, disease status, graft failure, PLT transfusion and PTR (Table S1 in Supporting Information). The multivariate analysis showed that the disease status (high risk), graft failure, more PLT transfusions and PTR were associated with TRM (Table 3).

OS

The PTR group had an inferior OS compared to the non-PTR group (47.9% vs. 76.3%, $P<0.001$) (Table 2, Figure 3A). In the univariate analysis, the age of the recipient, donor type, disease status, graft failure, number of PLT transfusions and PTR had effects on OS (Table S1 in Supporting Information). The results of the multivariate analysis indicated that disease status (high risk), graft failure and PTR were associated with OS (Table 3).

LFS

The PTR group had an inferior LFS than the non-PTR group (47.9% vs. 72.3%, $P<0.001$) (Table 2, Figure 3B). The univariate analysis showed that age of the recipient, donor type, disease status, graft failure, PLT transfusion and PTR were associated with LFS (Table S1 in Supporting Information). The multivariate analysis showed that disease status (high risk),