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Recombinant Human Thrombopoietin Promotes Platelet Engraftment and Improves Prognosis of Patients with Myelodysplastic Syndromes and Aplastic Anemia after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Poor platelet graft function (PPGF) is a significant complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, no optimal treatment has been recommended. This study investigated aspects of platelet recovery after allo-HSCT, including prognostic value and the effect of recombinant human thrombopoietin (rhTPO). We retrospectively analyzed 275 patients who received allo-HSCT in our center. Of them, 135 (49.1%) patients had good platelet graft function (GPGF) and 140 (50.9%) had PPGF. The latter included 59 (21.5%) patients with primary PPGF and 81 (29.4%) with secondary PPGF. Multivariate analysis showed that male gender ($P = .024$), lower $CD34^+$ cell count ($P = .04$), and no use of rhTPO ($P < .001$) were associated with PPGF. The 3-year overall survival rate of patients with PPGF (58%) was significantly less than that of patients with GPGF (82%; $P < .001$). We further analyzed the effect of rhTPO on prognosis of patients after allo-HSCT. Although no advantage was apparent when analyzing the entire cohort, for patients with myelodysplastic syndromes and aplastic anemia, rhTPO was associated with a significant survival advantage ($P = .014$).

INTRODUCTION

Thrombocytopenia is a significant complication after allogeneic (allo) hematopoietic stem cell transplantation (HSCT) and occurs in ~5% to 37% of allo-HSCT recipients [1-3]. Rapid and persistent recovery of platelet count after allo-HSCT reflects good platelet graft function (GPGF), but in many cases, platelet graft function is poor. Poor platelet graft function (PPGF) may be primary (failure to achieve initial reconstitution of the peripheral platelet count) or secondary (the count initially recovers, but later declines) [4]. Previous studies have suggested several factors that are associated with the development of PPGF after allo-HSCT, including donor match of the HLA or ABO (blood group system), intensity of the conditioning regimen, and stem cell source [5-7]. Patients with PPGF have an increased risk of bleeding and acute graft-versus-host disease (GVHD) [8-10]. These complications contribute to higher treatment-related mortality and poor prognosis [11,12].

To date, no standard treatment has been recommended for thrombocytopenia caused by poor graft function. A mainstay of treatment after allo-HSCT is platelet transfusion, but transfusion is associated with adverse effects such as infusion allergy, cardiac failure due to volume overload, and viral transmission [13]. In addition, prolonged transfusion requires significant hospital resources and costs and decreases patients' quality of life. Thrombopoietin (TPO) is a hematopoietic growth factor that stimulates the proliferation and differentiation of hematopoietic stem cells, primitive progenitors, megakaryocytes, and platelets [14-16]. In both in vitro and in vivo studies, TPO has proved to be the principal

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physiologic cytokine that stimulates platelet production [17-20]. The safety of recombinant human TPO (rhTPO) has been demonstrated in many previous trials [21-23]. A recent prospective randomized controlled trial from Peking University reported that rhTPO after haploidentical HSCT promoted platelet engraftment and reduced the requirement for platelet transfusion [24]. Subsequently, the same group reported a correlation between endogenous TPO levels and platelet recovery after allo-HSCT and the prognostic significance of TPO levels [25].

This present retrospective study investigated the prognostic value of platelet graft function after allo-HSCT. In addition, we analyzed the correlation between rhTPO and platelet engraftment, and we evaluated the clinical effect of rhTPO in specific diseases.

MATERIALS AND METHODS

Patient Characteristics

We retrospectively reviewed the medical records of patients who underwent their first allo-HSCT at First Affiliated Hospital of Soochow University from January 2013 to June 2014. Informed consent was obtained from the patients before data collection, in accordance with institutional guidelines, and the study was approved by the committees for the ethical review of research at First Affiliated Hospital of Soochow University. During the study period, 376 consecutive patients received allo-HSCT. In deference to the objectives of this study, the following patients were excluded: those who died within 3 months after HSCT and were therefore not available for evaluation of platelet graft function by our definition (n = 19) and those who received thrombopoietic agents other than rhTPO to promote platelet production (for example, interleukin 11; n = 53). In addition, 22 patients were excluded for disease relapse, because thrombocytopenia resulting from disease relapse was not defined as PPGF [11]. Another 7 patients were excluded because of a lack of complete data at follow-up. After excluding these patients, 275 patients were included in our final analysis. All patients were followed until death or until August 31, 2016.

Definitions

GPGF was defined as rapid recovery of platelet engraftment, with a persistent platelet count ≥50,000/μL without transfusion on or after day 90. PPGF included primary PPGF and secondary PPGF. Patients with *primary PPGF* were those who did not achieve initial platelet reconstitution, with persistent platelet counts <50,000/μL. *Secondary PPGF* was defined as a decline of platelet count to <50,000/μL for >7 consecutive days after initial platelet reconstitution. Patients with thrombocytopenia caused from graft rejection or disease recurrence were not considered to have PPGF, in accordance with the definition in a previous study [11]. The *date of platelet engraftment* was defined as the first day of 7 consecutive days with a platelet count of $\geq 20 \times 10^9$/L and without transfusion support. *Overall survival* (OS) was defined from the time of diagnosis until death from any cause or until the date of last follow-up.

Transplantation Procedure and GVHD Prophylaxis

At our center, all the donors received the same mobilizing protocol. Granulocyte colony–stimulating factor (5 μg/kg/day) was used to mobilize bone marrow and peripheral blood. The target mononuclear cell (MNC) counts were $\geq 6 \times 10^8$/kg of recipient weight. The target $CD34^+$ cell counts were $\geq 2 \times 10^6$/kg of recipient weight. Fresh and unmanipulated bone marrow and peripheral blood stem cells (retrieved on day 5 after granulocyte colony–stimulating factor) were infused into the recipient on the day of collection. Only when a small number of stem cells were collected and could not meet the need of target MNC and $CD34^+$ cell counts, an additional 1 or 2 days of mobilization were needed.

In our center, different stem cell sources were adopted in different transplantation types. For patients who received matched sibling donor transplants, bone marrow or peripheral blood derived stem cells were accepted, mainly dependent on the donor's decision. For patients who received haploidentical donor transplants, bone marrow stem cells (BMSC) were the first choice. For patients who received matched unrelated donor transplants, more than 85% received peripheral blood stem cells (PBSC) transplantation, mainly dependent on the donors' decision. For those who received BMSC plus PBSC, BMSC was the first choice. However, when small number of stem cells was collected, especially in those with mismatched ABO type compatibility between the donor and the recipient or older donors with poor mobilization, additional PBSCs were collected to meet the need of stem cell counts.

Most patients received a modified busulfan/cyclophosphamide regimen for myeloablative conditioning. This included patients with acute leukemia, myeloproliferative neoplasms, lymphoma, and part of myelodysplastic syndrome (MDS). For HLA-matched sibling transplantation, pretransplantation myeloablative conditioning regimens consisted of the following: semustine (250 mg/m^2, day –10), cytarabine (2 g/m^2/day, days –9 to –8), busulfan (3.2 mg/kg/day, days –7 to –5), and cyclophosphamide (1.8 g/m^2/day, days –4 to –3). For transplants from HLA-matched unrelated donors or haploidentical donors, patients received a regimen identical to that for HLA-matched sibling transplantation, except that doses of cytarabine were higher (4 g/m^2/day, days –9 to –8). In addition, patients receiving HLA-matched unrelated donor transplants also received hydroxycarbamide (80 mg/kg, day –10).

For patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria, and a proportion of MDS, the reduced-intensity conditioning regimen consisted of the following: semustine (250 mg/m^2, day –10), fludarabine (30 mg/m^2/day, days –10 to –6), cytarabine (1.5 g/m^2/day, days –10 to –6), and busulfan (3.2 mg/kg/day, days –5 to –3). For patients who received HLA-matched unrelated donor transplantations or haploidentical donor transplantations, antithymocyte globulin was used to prevent GVHD. All patients received GVHD prophylaxis consisting of cyclosporine, mycophenolate mofetil, and methotrexate.

Administration of rhTPO

The rhTPO (Recombinant Human Thrombopoietin Injection, SanSheng Pharmaceutical, Shenyang, China) was administered subcutaneously at a daily dose of 15,000 U from days +4 to +7 after transplantation. The subcutaneous injections were discontinued when the platelet count reached $\geq 50 \times 10^9$/L for 3 consecutive days. The administration of rhTPO was discontinued on day 21 if the platelet count had not recovered to 50×10^9/L.

Statistical Analysis

All analyses were performed using an SPSS software package (SPSS, Chicago, IL). The chi-square test and Mann-Whitney U test were used for categorical and continuous variables, respectively. Risk factors with $P < .05$ in the univariate analysis were chosen for further evaluation by multivariate logistic regression. Distributions of OS curves were estimated using the Kaplan-Meier method. OS rates were compared between groups using the log-rank test. Differences between groups were considered statistically significant if P values were <.05 in a 2-tailed test.

RESULTS

Patient Characteristics

A total of 376 consecutive patients received allo-HSCT during the study period. Of these, 275 patients were included in our analysis (Table 1) and the remainder were excluded for the following reasons: 53 patients received interleukin 11 therapy, 19 died within 3 months, 22 experienced disease relapse, and 7 were without complete data at follow-up. The median age of the included patients was 31 years (range, 3 to 60). Of the 275 patients who met the inclusion criteria, 216 (78.5%) achieved early platelet recovery; the remaining 59 (21.5%) patients had persistent platelet counts <50,000/μL and, therefore, were classified as having primary PPGF. Among the 216 patients with early platelet recovery, 135 (49.1%) maintained persistent platelet counts ≥50,000/μL for the entire observation period and, therefore, were considered to have GPGF, but 81 (29.4%) patients experienced a later platelet count decline to <50,000/μL and were considered to have secondary PPGF.

The correlation between clinical variables and the use of rhTPO is shown in Table 1. Patients who were diagnosed with MDS or AA had a higher incidence of using rhTPO. In addition, patients who received haploidentical donor transplants used rhTPO in higher frequency. Based on the outcome of platelet engraftment, patients with GPGF also had a higher frequency of using rhTPO (Table 1). No significant correlation was found between other clinical variables and the use of rhTPO.

Risk Factors for PPGF

The univariate analysis showed that patients of male gender, lower $CD34^+$ cell count, and no use of rhTPO were