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Posttransplant Thrombopoiesis Predicts Survival in Patients Undergoing Autologous Hematopoietic Progenitor Cell Transplantation

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ABSTRACT

The frequency and clinical significance of secondary thrombocytopenia following initial engraftment in autologous hematopoietic progenitor cell transplantation (HPCT) is unknown. An institutional review board approved retrospective study of thrombopoiesis was performed in 359 patients transplanted with autologous blood (97%) or marrow (3%) who achieved platelet engraftment to >50,000/μL. Idiopathic secondary post-transplant thrombocytopenia (ISPT) was defined as >50% decline in blood platelets to <100,000/μL in the absence of relapse or sepsis. ISPT occurred at a median of day +35 posttransplant in 17% of patients. Patients with ISPT had similar initial platelet engraftment (median 17 days) versus non-ISPT patients (18 days; *P* = NS) and recovered platelet counts (median 123,00 K/μL) by day 110 posttransplant. Four factors were independently associated with post-transplant death in a multivariate model: disease status at transplant; the number of prior chemotherapy regimens, failure to achieve a platelet count of >150,000/μL posttransplant, and the occurrence of ISPT. A prognostic score was developed based upon the occurrence of ISPT and posttransplant platelet counts of <150,000/μL. Survival of patients with both factors (n = 25) was poor (15% alive at 5 years); patients with 1 factor (n = 145) had 49% 5-year survival; patients with 0 factors (n = 189) had 72% 5-year survival. Patients who failed to achieve a platelet count of >150,000/μL received significantly fewer $CD34^+$ cells/kg (*P* < .001), whereas patients with ISPT received fewer $CD34^+CD38^-$ cells/kg (*P* = .0006). The kinetics of posttransplant thrombopoiesis is an independent prognostic factor for long-term survival following autologous HPC. ISPT and lower initial posttransplant platelet counts reflect poor engraftment with long-term and short-term repopulating $CD34^+$ hematopoietic stem cells, respectively, and are associated with an increased risk of death from disease relapse.

KEY WORDS

Thrombopoiesis • Stem cells • Platelets • Thrombocytopenia • Autologous transplantation

INTRODUCTION

Profound thrombocytopenia occurs in all patients following myeloablative conditioning and autologous stem cell rescue, and reflects bone marrow aplasia induced by high-dose chemotherapy and/or total body irradiation (TBI). Following autologous hematopoietic progenitor cell transplantation (HPCT), restoration of normal numbers of blood leukocytes and platelets usually follows predictable kinetics within the first month posttransplant, with increasing numbers of granulocytes, platelets, lymphocytes, and finally erythrocytes in the blood. The kinetics of granulocyte recovery have been extensively studied in autologous transplant recipients leading to identification of the minimum and optimal numbers of $CD34^+$ hematopoietic progenitors necessary for predictable reestablishment of hematopoiesis [1-3]. Higher numbers of CD34 cells in the graft are associated with more rapid neutrophil and platelet engrafment [4-6] but not necessarily better long-term outcomes [7]. The recovery of a higher number of blood lymphocytes early post-transplant has been reported to be associated with

improved posttransplant survival, and appears to be correlated with transplantation of larger numbers of lymphocytes in the hematopoietic graft rather than de novo lymphopoiesis from lymphocyte progenitors in the graft [8-12].

In contrast, studies of the kinetics of platelet recovery following HPCT have largely been limited to descriptions of the time from transplant to the day of independence from platelet transfusions. Most reports describing clinical outcomes following autologous transplantion have compared the median time the blood platelet counts reached 20,000/μL or 50,000/μL without tranfusion support [13]. Although the availability of myeloid and erythroid growth factors offer safe and effective management strategies for mitigating posttransplant neutropenia and anemia, respectively, similar agents are not currently commercially available for the management of posttransplant thrombocytopenia [14]. Thus, the platelet count following autologous HPCT represents a direct indicator of the hematopoietic activity of the graft.

A subset of patients who initially recover platelet counts after transplantation experience subsequent secondary posttransplant thrombocytopenia (SPT), or varying duration, and because of different mechanisms [15]. Sepsis or relapse may result in early SPT; SPT occurring 6-12 months posttransplantation has been managed with steroids and immune globulin, drugs that are used to treat patients with idiopathic thrombocytopenia purpura [16,17]. The phenomenon of idiopathic secondary posttransplant thrombocytopenia (ISPT), ocurring within the first 100 days posttransplant, has not been well defined.

To define the incidence of ISPT, its association with pre- and posttransplant variables, the kinetics of platelet production following autologous transplantation, and the prognostic significance of posttransplant thrombopoiesis, we undertook a retrospective study of platelet production in consecutive patients undergoing autologous HPCT at a single institution. We hypothesized that an idiopathic secondary decline in blood platelet counts following initial engraftment would be associated with transplantation of a hematopoietic graft containing fewer numbers of phenotypically undifferentiated $CD34^+$ $CD38^-$ hematopoietic progenitors [18,19] responsible for long-term repopulating activity [20].

METHODS

Study Design and Definitions

We performed a single institution retrospective cohort study on platelet engraftment kinetics and survival among consecutive patients undergoing high-dose chemotherapy and autologous hematopoietic progenitor cell transplantation. The day of granulocyte engraftment was defined as the first of 3 consecutive days on which patients had an absolute granulocyte count of at least 500/μL. The day of platelet engraftment was defined as the day platelet counts ≥50,000/μL were achieved without a platelet transfusion in the previous 7 days. Because there are no existing descriptions of the phenomena of SPT (outside of late posttransplant thrombocytopenia), SPT was defined as a clinically significant drop in platelet count, of at least a 50% absolute decrease, to a value <100,000/μL after initial platelet engraftment achieved. ISPT was defined as SPT within the first 100 days posttransplant in the absence of relapse or sepsis. Demographics of the patients, their diagnoses, conditioning regimens, and characteristics of their grafts were entered into a study-specific, institutional review board (IRB)-approved database along with blood counts, transfusions, and infections occurring within the first 100 days posttransplant. Follow-up survival data was available for surviving study subjects for a median of 2 years posttransplant.

Study Subjects

The study set was derived from 509 consecutive cancer patients who underwent high-dose chemotherapy and autologous blood (97%) or bone marrow (3%) HPC transplantation between January 1997 and June 2005. An IRB-approved waiver of consent was granted for the conduct of this study. Forty patients had insufficient data on posttransplant platelet counts to assess engraftment, 6 patients died prior to engraftment (1% early death), and 18 patients did not achieve a platelet count of >50,000/μL by day +100 (4% failure to achieve platelet engraftment). Three hundred fifty-nine of the 445 remaining patients (81%) had data on the $CD34^+$ cell subsets in the autograft and constituted the study cohort. Survival was documented at posttransplant follow-up visits, or by contacting the patient or referring oncologist. The date of death was confirmed using Social Security Death Index data. The primary cause of death was available for 78% of deceased patients. Treatment regimens were defined as chemotherapy protocols given as part of a planned course of therapy (ie, ABVD); induction chemotherapy and mobilization with 1 cycle of cyclophosphamide given at the end of 1 course of therapy (ie, VAD) was considered to be a single regimen.

Statistical Methods

All statistical analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL). Comparisons between mean values occurred using a Student's *t*-test. Comparisons of ordinal characteristics between ISPT and controls were performed using a chi-square test. Survival differences between subgroups were compared using the Kaplan-Meier estimate of survival and