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Efficacy of CD34$^+$ Stem Cell Dose in Patients Undergoing Allogeneic Peripheral Blood Stem Cell Transplantation after Total Body Irradiation

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ABSTRACT

We estimated the effect of CD34$^+$ stem cell dose during peripheral blood stem cell transplantation (PBSCT) in predicting mortality after total body irradiation (TBI). Between 1997 and 2004, 146 consecutive patients with hematologic malignancies received fractionated TBI (12-13.6 Gy) in 8 fractions over 4 days before undergoing PBSCT; 61 patients received TBI with reduced radiation dose to the lung (6-9 Gy). The number of CD34$^+$ cells transplanted was recorded for all patients. A cubic spline representation for CD34$^+$ dose within a Cox proportional hazards model was used to model the relationship between the CD34$^+$ dose and mortality. Median follow-up was 44 months (range, 12–90 months). The CD34$^+$ cell dose ranged from 2.45 to 15.90 × 10^6 cells/kg (median, 5.15 × 10^6 cells/kg). Risk of mortality decreased with CD34$^+$ doses between 4–8 × 10^6 cells/kg and then began to increase. For all patients, CD34$^+$ doses of 5.1–12.9 × 10^6/kg resulted in at least a doubling of median survival associated with the lowest CD34$^+$ value. In patients treated with lung dose reduction, a similar range of CD34$^+$ dose (4.3–10.2 × 10^6 cells/kg) produced at least a 5-fold improvement from the survival associated with the lowest CD34$^+$ dose; however, the relationship between CD34$^+$ dose and mortality was not statistically different when analyzed by lung dose reduction. A method for assessing risk of mortality by CD34$^+$ dose as a continuous variable is presented. Risk of mortality decreased with CD34$^+$ doses between 4-8 × 10^6 cells/kg and then began to increase.

KEY WORDS

CD34$^+$ dose • Lung shielding • Lung dose reduction • Peripheral blood stem cell transplantation • Total body irradiation

INTRODUCTION

Peripheral blood stem cell transplantation (PBSCT) is a key component in the treatment of various malignancies [1-5]. Preparatory regimens for PBSCT often include total body irradiation (TBI) [5-7]. Increasing numbers of CD34$^+$ stem cells given during transplantation are reported to correlate with decreasing time to engraftment [8-10]. This effect is retained until a given threshold dose, beyond which no extra benefit occurs [10]. Relatively higher CD34$^+$ doses are reported to be associated with increased incidence of chronic graft-versus-host disease (GVHD) [11-13]; however, the effect of relatively higher CD34$^+$ stem cell dose on survival remains unclear [12-15].

A preliminary analysis of this cohort, using the median dose as a cutpoint, showed that CD34$^+$ cell dose was a risk factor for pulmonary transplantation–related mortality (relative risk [RR] = 9.4 for a CD34$^+$ dose $< 5 \times 10^6$ cells/kg [16]. Lung dose–reduced TBI has also been shown to improve survival in certain patients with poor pretreatment pulmonary function test values [17].

The present analysis was performed to estimate the effect of CD34$^+$ stem cell dose (as a continuous variable) during PBSCT in predicting all-cause mortality after TBI performed with or without dose reduction to the lung.

METHODS

Study Group

Between July 1997 and August 2004, 146 consecutive patients with hematologic malignancies under-

went T-cell–depleted PBSCT from a HLA-identical sibling in 5 successive National Heart, Lung, and Blood Institute Institutional Review Board–approved protocols (97-H-0099, 99-H-0046, 02-H-0111, 03-H-0192, and 04-H-0112).

Conditioning Regimens

Three conditioning regimens were used in consecutive time periods. Regimen A (April 1997-December 2001) consisted of 13.6 Gy of TBI and cyclophosphamide 120 mg/kg, with no lung dose reduction (n = 85). Regimen B (February 2002-May 2003) consisted of 12.0 Gy of TBI, with 9.0 Gy to the lungs, cyclophosphamide 120 mg/kg, and fludarabine 125 mg/m^2 (n = 35). Regimen C (June 2003-August 2004) consisted of 12.0 Gy of TBI, with 6.0 Gy to the lungs, cyclophosphamide 120 mg/kg, and fludarabine 125 mg/m^2 (n = 26).

Radiation Techniques

The radiation techniques used in this cohort have been described previously [17].

Transplantation Approach

In the first protocol, patients received a T-cell–depleted granulocyte colony-stimulating factor (G-CSF)-mobilized PBSCT using the Ceprate selection system (CellPro, Bothell, WA). Subsequent protocols used an Isolex 300 cell separator (Baxter, Deerfield, IL), as described previously [18]. CD34$^+$ cells were positively selected using anti-CD34$^+$ beads, and residual T cells were removed with a cocktail of anti-CD2, -CD6, and -CD7 antibody–coated beads. The CD34$^+$ cell dose ranged from 2.45 to 15.90 $\times$ 10^6/kg (median, 5.15 $\times$ 10^6/kg); the T-cell dose was 0.2-1.0 $\times$ 10^5 CD3$^+$ cells/kg recipient weight. In the absence of GVHD or unless molecular remission was documented in chronic myeloid leukemia, T cells were added back on days 45 and 100 (n = 140) or on day 60 (n = 6). The cyclosporine (CSA) dose varied according to protocol; 36 patients received standard-dose CSA (target plasma level, 200-400 ng/mL), 20 received low-dose CSA (target plasma level, 100-200 ng/mL) starting on day −4 and continuing until an oral dose was tolerated, and 90 received no CSA during the first 6 weeks after transplantation. All patients started CSA either on day 44 (if T cells were added back on day 45) or on day 59 (if T cells were added back on day 60), and it was continued until at least day 130 (or longer, if chronic GVHD [cGVHD] occurred). Standard prophylaxis against infection included fluconazole to day 100, co-trimoxazole for 6 months, and weekly surveillance for cytomegalovirus antigenemia, as described previously [18,19]. Acute GVHD (aGVHD) was managed with high-dose steroids. Steroid-refractory patients (ie, no response to 7 days of treatment) received combined treatment with anti–tumor necrosis factor (infliximab) and anti-CD25 (daclizumab) monoclonal antibodies, as described previously [20].

Statistical Methods

We sought to estimate the relationship between CD34$^+$ dose and mortality in a flexible way. Standard approaches, such as Cox proportional hazards models with linear effects, make strong assumptions about the form of the relationship between CD34$^+$ dose and mortality (ie, that a change of 1 unit in CD34$^+$ dose will have the same relative effect on mortality for any value of CD34$^+$ dose). Therefore, the relationship of CD34$^+$ dose as a continuous variable and mortality was modeled with a cubic spline representation for CD34$^+$ dose within a Cox proportional hazards model [21]. This approach allows for a smoothed representation of a continuous relationship between CD34$^+$ dose and mortality. The cubic spline terms were fit with 2 knot points, which allowed for sufficient flexibility with this relatively small sample size. We sought to estimate the relationship between risk of mortality and CD34$^+$ dose. Models were fit on (1) the whole patient group and (2) by whether or not patients received lung dose–reduced TBI.

Formal statistical inference was done using likelihood ratio tests. We tested for a relationship between CD34$^+$ dose and mortality using a χ^2 test with 3 degrees of freedom, both with and without adjustment for other potential prognostic variables. We formally tested for whether the relationship between CD34$^+$ dose and mortality varied depending on other factors, such as lung dose–reduced TBI, combined ventilation/diffusion capacity (CVDC) deficit (defined as having both a forced expiratory volume in 1 minute [FEV$_1$] and diffusing capacity of the lung for CO [DLCO] of $<$ 100% predicted), and age at transplantation by testing for a statistical interaction between the spline terms of CD34$^+$ and these other factors.

Curves of the log hazard ratio (HR), relative to the CD34$^+$ dose corresponding to the worst survival in that group, were estimated. Efficacious CD34$^+$ ranges were defined as those corresponding to an HR of $<$ 0.5 (−0.69 on the log scale) relative to the lowest CD34$^+$ dose in that group (ie, worst survival). This range corresponds to a doubling of the median survival relative to the lowest CD34$^+$ dose. For the lung dose reduction group, we also present an efficacious CD34$^+$ dose region corresponding to a 5-fold increase in median survival, because the efficacious region based on a 2-fold increase was too wide to be useful.

Summary statistics, such as sample proportions, medians, standard deviations, and 95% confidence intervals, were used to describe the patient characteristics and the 1-year survival probabilities for patients in