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EBMT Risk Score Predicts Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients Who Have Failed a Previous Transplantation Procedure

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Increasing numbers of allogeneic hematopoietic stem cell transplantation (allo-SCT) are being performed for patients who have failed a previous allogeneic or autologous SCT. We investigated whether the EBMT risk score could predict outcome after a subsequent allo-SCT. We analyzed prognostic factors in 124 consecutive patients who underwent a second transplantation using an allogeneic donor at our institution. Patients with either a first autologous (N = 64) or first allogeneic (N = 60) SCT were included. Age, disease stage, time interval from diagnosis to transplantation, donor type, and donor–recipient sex combination were used to establish a score from 0 to 7 points, from which 3 groups were identified. The 5-year survival probability decreased from 51.7% for risk scores 0-3 (low, n = 25), to 29.3% for risk score 4 (intermediate, n = 42), and only 10.4% for risk scores 5-7 (high, n = 57), $P = .001$. We propose that the EBMT risk score can identify patients most likely to benefit from a second transplantation.

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INTRODUCTION

Relapse is the most frequent cause of treatment failure after allogeneic (allo-) or autologous (auto-) hematopoietic stem cell transplantation (SCT). Several studies have shown that a subsequent allo-SCT procedure may be an effective salvage intervention with a probability of disease-free survival (DFS) ranging from 11% to 44%, and relapse rates of 25% to 75% [1-14]. Given that relapse after transplantation has a dismal prognosis, and that selected patients can remain alive and disease-free after a subsequent allo-SCT, identification of prognostic factors that determine more reliably the patient group most likely to benefit would be valuable.

In 1998, the European Group for Blood and Marrow Transplantation (EBMT) defined a risk score for patients with chronic myeloid leukemia (CML), the most frequent indication for an allo-SCT at that time [15]. The risk score was based on 5 criteria: disease stage, patient age, donor type, interval from diagnosis to transplantation, and donor–recipient sex combination. The score was validated in several independent CML patient cohorts as well as for other hematologic malignancies [16].

Here we investigated the prognostic value of the EBMT risk score to predict the outcome of subsequent allo-SCT in patients with hematologic malignancies who have failed a first transplantation. We demonstrated that the five well-defined pretransplantation patient and donor characteristics that make up the EBMT risk score, together with the interval between first and second SCT, are independent predictors of nonrelapse mortality (NRM) and overall survival (OS).

MATERIALS AND METHODS

Patient Population

We performed a retrospective analysis of the outcomes of transplantation in 124 consecutive patients who underwent a second SCT using an allogeneic donor between October 1985 and July 2010, after prior allogeneic (n = 60) or autologous (n = 64) SCT. All

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patients gave written informed consent for the use of their data for the analysis.

EBMT Risk Score

The EBMT risk score was calculated based on 5 pretransplantation variables: age of the patient, disease stage, time from diagnosis to transplantation, donor type, and donor–recipient sex combination, with 0, 1, or 2 points for each factor [15]. Age was categorized as <20 years (0), 20 to 40 years (1), and >40 years (2). The stage of disease applied to our patient population at the time of second SCT was as follows: Early disease stage (0) was limited to patients with CML who had relapsed after a prior auto- or allo-SCT and remained in chronic phase. All other patients were, by definition, scored as intermediate- or late-stage disease. Intermediate disease stage (1) included: acute leukemia in second complete remission CML in all other stages than chronic phase or blast crisis myelodysplastic syndrome (MDS) in second complete remission or in partial remission; and non-Hodgkin lymphoma (NHL) and multiple myeloma in second complete remission, in partial remission, or stable disease. Late-stage disease (2) included: acute leukemia in all other disease stages, CML in blast crisis, MDS in all other disease stages, and multiple myeloma and lymphoma in all other disease stages than those defined as early or intermediate. Time from first diagnosis to second transplant was categorized into <12 months (0) and >12 months (1). Donor type separated HLA-identical sibling transplants (0) from unrelated donor transplants and mismatched family donors (1). Donor–recipient sex combination separated all others (0) from the male recipient with a female donor (1). Hence, the score ranged from 0 to a maximum of 7 risk points.

Statistical Analysis

Two outcomes were considered: OS and NRM. Probability curves were calculated using the Kaplan-Meier method for survival and the cumulative incidence procedure for NRM. Outcomes were calculated relative to the date of second transplantation, until the event of interest, or until the date of last follow-up. Groups were compared using the log-rank test, and factors found to be significant at the $P < .1$ level were entered into a Cox regression analysis. All analyses were performed using SPSS version 17 software (SPSS, Inc., Chicago, IL). All statistical tests were 2 sided, and $P < .05$ was used to indicate statistical significance.

RESULTS

Patient Characteristics

The patient characteristics are summarized in Table 1. The median interval between first and second SCT was 20 months. Patients were more likely to have a longer interval to second SCT if they had a diagnosis of CML (38 of 57) compared with patients with acute leukemia and MDS (11 of 25), myeloma (7 of 22), or NHL (7 of 17) ($P = .038$). At second SCT, donors were HLA-identical siblings (n = 66, 53.2%), matched unrelated donors (n = 41, 33.1%), mismatched unrelated donors (n = 8, 6.5%), and nonidentical family donors (n = 9, 7.2%). The source of the graft was peripheral blood stem cells (PBSC) (n = 60, 48.4%) and bone marrow (BM) (n = 64, 51.6%). Of 61 patients who relapsed following a previous allo-SCT, 41 received stem cells from the same donor, 13 from a different donor, and in 7 this information was not available. Conditioning intensity was classified into reduced intensity (RIC) (n = 52; 41.9%) or myeloablative (MAC) (n = 72; 58.1%). In 37 of 52 (71%) patients who received an RIC second transplant, the preparative regimen was fludarabine based (in combination with cyclophosphamide, busulphan, or melphalan). Of 72 patients who received an MAC conditioned transplant, 29 (40%) received total body irridiation (TBI) (1320 or 1400 cGy), and in 28 (39%) the preparative regimen was busulphan based (16 mg/kg orally). In vivo T cell depletion with alemtuzumab was used in 83 of 124 recipients (66.9%). At the time of the analysis, 29 of 124 patients were alive (23.4%), and 95 had died (76.6%) (73 from transplant-related causes and 22 of their disease). Transplant-related causes of mortality included infection in 41, graft-versus-host disease (GVHD) in 8, graft failure in 3, and other transplant-related causes including veno-occlusive disease (VOD), pneumonitis, acute respiratory distress syndrome (ARDS), and multiorgan failure in 21 patients. Median survival was 9.6 months. For the entire group, the probability of survival at 5 years was 25.4% (95% confidence interval [CI]: 18%-34%) with an estimated cumulative incidence of NRM at 1 year of 45.0% (95% CI: 37%-55%).

EBMT Risk Score at Second SCT

The EBMT score was calculated for each patient at second SCT, based on the factors outlined above (Table 2). EBMT risk scores of 0 to 7 points were assigned to each patient, and because of low numbers of patients with some scores, 3 combined groups were identified (Table 2B).

The survival probability at 5 years decreased from 51.7% (95% CI: 33%-70%) for risk scores 0-3 (low, n = 25), to 29.3% (95% CI: 17%-47%) for risk score 4 (intermediate, n = 40), and only 10.4% (95% CI: 4%-24%) for risk scores 5-7 (high, n = 57), $P = .0003$ (Figure 1A), whereas 1-year NRM rates increased from 28.03% (95% CI: 15-53; risk score, 0-3) to 33.2% (95% CI: 21-52; risk score, 4) and 58.8% (95% CI: 47-73; risk score, 5-7), $P = .0003$