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Outcome and Prognostic Factors for Patients Who Relapse after Allogeneic Hematopoietic Stem Cell Transplantation

Gita Thanarajasingam [1], Haesook T. Kim [2], Corey Cutler [3], Vincent T. Ho [3], John Koreth [3], Edwin P. Alyea [3], Joseph H. Antin [3], Robert J. Soiffer [3], Philippe Armand [3,*]

[1] Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Minnesota
[2] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts
[3] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

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A B S T R A C T

Disease relapse remains a major obstacle to the success of allogeneic hematopoietic stem cell transplantation (HSCT), yet little is known about the relevant prognostic factors after relapse. We studied 1080 patients transplanted between 2004 and 2008, among whom 351 relapsed. The 3-year postrelapse overall survival (prOS) rate was 19%. Risk factors for mortality after relapse included shorter time to relapse, higher disease risk index at HSCT, myeloablative conditioning, high pretransplantation comorbidity index, and graft-versus-host disease (GVHD) occurring before relapse. Important prognostic factors did not vary by disease type. Based on this, we could stratify patients into 3 groups, with 3-year prOS rates of 36%, 14%, and 3% ($P < .0001$). This score was validated in an historical cohort of 276 patients. Postrelapse donor lymphocyte infusion or repeat HSCT was associated with improved prOS, as was the development of GVHD after relapse. These differences remained significant in models that accounted for other prognostic factors and in landmark analyses of patients who survived at least 2 months from relapse. The results of this study may aid with prognostication and management of patients who relapse after HSCT and motivate the design of clinical trials aimed at relapse prevention or treatment in higher-risk patients.

INTRODUCTION

Advances in allogeneic hematopoietic stem cell transplantation (HSCT) have improved the safety of the procedure and significantly broadened its applicability. Despite this, disease relapse still represents a major barrier to success for patients transplanted for hematologic malignancies. In fact, relapse is the principal cause of treatment failure for patients undergoing reduced-intensity conditioning (RIC) or nonmyeloablative HSCT. Much work has focused on identifying factors at the time of HSCT that increase the risk for relapse and on devising strategies for its prevention and management [1-8], but little is known about the determinants of outcome after relapse. Recent studies, notably from the European Group for Blood and Marrow Transplantation, describe the outcomes in subgroups of relapsing patients, especially patients with acute leukemia receiving RIC HSCT [9-11], but no study has yet identified the factors that influence survival after relapse in broader cohorts of patients across multiple disease and transplantation types. This information is necessary both to assess the prognosis of patients who relapse after HSCT and to optimally select patients for clinical trials of postrelapse treatment strategies.

We therefore undertook an observational study of 1080 consecutive adult patients with hematologic malignancies who underwent HSCT at Dana-Farber Cancer Institute/Brigham and Women's Hospital between 2004 and 2008, with the following goals: (1) elucidating the important prognostic factors after relapse, (2) determining whether those factors are disease-specific or whether the disease risk itself is an independent prognostic factor, and (3) describing the outcome of various postrelapse intervention strategies. Three-hundred fifty-one patients (33%) relapsed and form the basis of this report. We determined prognostic factors for postrelapse overall survival (prOS), devised a simple risk score to stratify patients into different risk groups for prOS, validated this score in an historical control population, and examined the impact of postrelapse strategies on outcome.

METHODS

Patients

We analyzed consecutive adult patients who underwent their first HSCT with myeloablative conditioning (MAC) or RIC at Dana-Farber Cancer Institute/Brigham and Women's Hospital within the 4-year period from 2004 to 2008. Patients receiving transplantation for benign hematologic conditions were excluded. Individual medical records of all relapsed patients (defined as progression or relapse of disease any time after HSCT) were examined. Molecular or cytogenetic relapses were not considered as relapse events.

We collected data on comorbidities necessary to calculate the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) [12], when available. Comorbidity information was extracted retrospectively for patients who underwent HSCT between 2005 and 2007 and prospectively collected for patients who underwent HSCT after 2007. Disease Risk Index (DRI) was assigned as previously described [13], using the latest available tumor cytogenetics information for patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The DRI accounts for disease risk, including cytogenetics risk for AML and MDS, and for disease status at the time of transplantation, in general separating patients in complete or partial remission from those with active disease.

To validate the postrelapse risk score, we used an historical control cohort of 869 patients who received their first HSCT between 1998 and 2003, among whom 32% relapsed. Institutional review board approval was obtained from the Office for Human Research Studies of the Dana-Farber/Harvard Cancer Center to conduct this study.

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* Correspondence and reprint requests: Philippe Armand, MD, PhD, Dana-Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215.
E-mail address: parmand@partners.org (P. Armand).

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Transplantation

Patients were transplanted on a variety of treatment plans and investigational protocols. MAC regimens consisted mostly of cyclophosphamide (3600 mg/m^2 or 120 mg/kg) plus total body irradiation (1400 cGy in 7 fractions) or busulfan (12.8 mg/kg intravenously) plus cyclophosphamide (3600 mg/m^2). RIC regimens consisted principally of fludarabine (120 mg/m^2) plus intravenous low-dose busulfan (3.2 to 6.4 mg/kg). Patients received bone marrow or peripheral blood stem cells from HLA-matched or mismatched, related or unrelated donors, or double umbilical cord blood units. Graft-versus-host disease (GVHD) prophylaxis consisted mostly of tacrolimus combined with methotrexate, with or without sirolimus.

Supportive care for all patients followed institutional standards. The practice at our center is to attempt immunosuppression withdrawal in all patients at relapse, except for patients whose condition makes it unlikely they would survive for more than a few weeks or for whom the severity and activity of GVHD contraindicates immunosuppression withdrawal.

Donor lymphocyte infusion (DLI) is generally attempted when patients are immunosuppression-free without significant GVHD, with more than about 20% donor chimerism, and when DLI can be obtained from the donor. In cases where no DLI can be obtained or donor chimerism is too low, patients are considered for repeat HSCT. This practice did not change over the course of the study.

Statistical Analysis

Patient baseline characteristics were reported descriptively. prOS was defined as the time from documentation of relapse or progression to death from any cause and calculated using the Kaplan-Meier method. Patients who were alive or lost to follow-up were censored at the time last seen alive. The log-rank test was used for comparisons of Kaplan-Meier curves. Potential prognostic factors for OS were examined in the proportional hazards model; in the multivariable models, variables were added by stepwise selection (see Table 2 for variables considered).

The proportional hazards assumption for each variable of interest was tested and interaction terms examined. The linearity assumption for continuous variables was examined using restricted cubic spline estimates of the relationship between the continuous variable and log relative hazard, and the cut-off points of these variables were based on the change of the log relative hazards.

All P values are 2-sided with a significance level of .05. The c-statistic [14] was used to compare model fit using the Hmisc package in R (the CRAN project, R Foundation for Statistical Computing, Vienna, Austria). To build a risk score, points were assigned roughly following the hazard ratio for prOS in the multivariable model. The only exception was for high/very high DRI, which was assigned an integral number of points to keep the score simple. All calculations were done using SAS 9.3 (SAS Institute, Cary, NC) and R version 2.13.2 (the CRAN project, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

Among the 1080 studied patients, 351 (33%) relapsed at a median time of 4.5 months (range, 0 to 59) after HSCT. Their characteristics are listed in Table 1. The median age was 52 years (range, 19 to 71). Most had intermediate- or high-risk disease by DRI. Two thirds had received a RIC HSCT. Seventy-two percent were on immunosuppression at the time of relapse (51% for GVHD prophylaxis and 21% for GVHD treatment). In all, 35% had had GVHD before the time of relapse.

Prognostic Factors for Postrelapse Survival

Table 2 shows the results of univariable and multivariable analyses for prOS among the 351 relapsed patients. In univariable analyses, variables associated with inferior prOS were higher DRI, shorter time to relapse (TTR), MAC, and HCT-CI of 3 or above. The 3-year prOS rate for patients who underwent MAC was 10%, compared with 23% for those who received an RIC HSCT (P = .002). In addition, being on immunosuppression at the time of relapse was associated with worse prOS. Because TTR was the most important prognostic factor, we examined its association with other important baseline variables. A shorter TTR was associated with higher DRI, older age, and RIC. We compared the prognostic value of the DRI with that of 2 other possible classification schemes: myeloid versus lymphoid and the low-risk/high-risk system used in a recent Blood and Marrow Transplant Clinical Trials Network trial [15]. The c-statistic was highest for the DRI, which we therefore retained as the risk stratification scheme for further analyses.

In multivariable analyses, the same factors remained significant except for being on immunosuppression at the time of relapse (hazard ratio [HR] for mortality = .8, P = .4); instead, the occurrence of GVHD (acute or chronic) before relapse was associated with significantly inferior prOS in the multivariable models. This discrepancy can be explained by the strong association between being on immunosuppression, history of GVHD, and time of relapse, the latter of which remained very strongly associated with prOS in the multivariable models. Patients who relapsed earlier were more likely to be on immunosuppression at the time of relapse (95% of patients who relapsed within 3 months were still on immunosuppression, compared with 87% of those who relapsed within 3 to 6 months, 47% of those who relapsed within 6 to 24 months and 18% of those who relapsed after 2 years, $P < .0001$). Conversely, patients who relapsed earlier were less likely to have had prior or active GVHD at the time of relapse (15% among those with TTR < 3 months, 27% for 3 to 6 months, 53% for 6 to 24 months, and 77% for >24 months, $P < .0001$), which likely explains why GVHD was not significant in the univariable models, even when only grades III or IV acute GVHD was considered. GVHD was an adverse factor for prOS in the multivariable models regardless of the type of GVHD (acute versus chronic) or whether the GVHD was active or not at the time of relapse. There were no relevant significant interactions between prognostic variables in the multivariable models.

We obtained similar results in multivariable models built separately for MAC and RIC patients, although the impact of the DRI was less pronounced among patients who received MAC. Because RIC was associated with shorter TTR in this cohort, which could inflate the apparent benefit of RIC in the prOS multivariable model, we also checked models that did not include TTR; RIC remained significantly associated with superior prOS even in those models (HR for mortality associated with RIC = .7; P = .022).

Prognostic Score for prOS

We constructed a simple score using the significant factors established previously (Table 3). Because the HR associated with a high HCT-CI was only 1.4 and because the addition of the HCT-CI to the model did not noticeably improve model fit (c-statistic of model with HCT-CI .680 versus .675 for a model without HCT-CI), it was not included in the score. The score can be calculated by summing the points for a given patient among TTR (1 point for 6 to 24 months, 2 for 3 to 6 months, 3 for <3 months), DRI (1 point for intermediate, 2 for high/very high index), conditioning intensity (1 point for myeloablative), and prior GVHD (1 point). This score stratified the cohort into 3 groups with very different prOS rates (Figure 1A and Table 3). Patients with 0 to 3 points had a 3-year prOS rate of 36%, patients with 4 points a 3-year prOS rate of 14%, and patients with 4 to 7 points a 3-year prOS rate of 3%. Among the low-risk group, 46 patients (13% of the total population) had fewer than 3 risk factors and a 3-year prOS rate of 51%. Because this is a surprisingly high survival rate, we examined the characteristics of this group: 65% were 50 years or older; only 4% had relapsed within 6 months of HSCT, whereas 67% had relapsed within 6 to 24 months of transplant and 28% had