Biol Blood Marrow Transplant 23 (2017) 1523–1530

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Personalized Prognostic Risk Score for Long-Term Survival for Children with Acute Leukemia after Allogeneic Transplantation

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Article history:
Received 18 April 2017
Accepted 10 May 2017

Key Words:
Survival
Risk score
Transplantation
Acute myeloid leukemia
Acute lymphoblastic leukemia

A B S T R A C T

We studied leukemia-free (LFS) and overall survival (OS) in children with acute myeloid (AML, n = 790) and acute lymphoblastic leukemia (ALL, n = 1096) who underwent transplantation between 2000 and 2010 and who survived for at least 1 year in remission after related or unrelated donor transplantation. Analysis of patient-, disease-, and transplantation characteristics and acute and chronic graft-versus-host disease (GVHD) was performed to identify factors with adverse effects on LFS and OS. These data were used to develop risk scores for survival. We did not identify any prognostic factors beyond 4 years after transplantation for AML and beyond 3 years for ALL. Risk score for survival for AML includes age, disease status at transplantation, cytogenetic risk group, and chronic GVHD. For ALL, the risk score includes age at transplantation and chronic GVHD. The 10-year probabilities of OS for AML with good (score 0, 1, or 2), intermediate (score 3), and poor risk (score 4, 5, 6, or 7) were 94%, 87%, and 68%, respectively. The 10-year probabilities of OS for ALL were 89% and 80% for good (score 0 or 1) and poor risk (score 2), respectively. Identifying children at risk for late mortality with early intervention may mitigate some excess late mortality.

INTRODUCTION

The majority of the morbidity and mortality after allogeneic hematopoietic cell transplantation in children with acute leukemia occurs in the first year after transplantation [1-6]. Many factors may influence the prognosis of children with acute leukemia, including clinical features at diagnosis (white

Financial disclosure: See Acknowledgments on page 1529.
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http://dx.doi.org/10.1016/j.bbmt.2017.05.011
1083-8791/

blood cell count and cytogenetic risk), time to and the duration of first complete remission (CR), disease status at transplantation, and post-transplantation complications, such as graft-versus-host disease (GVHD), infection, and end-organ toxicity [7-12]. When a child reaches the landmark of 1 or 2 years after transplantation and is in remission, parents ask about long-term survival, wondering about the risk of recurrent leukemia, transplantation-related complications such as chronic GVHD and end-organ damage, and the likelihood of long-term survival. Data on long-term survival in children are limited, as most reports have focused on adults [7,9]. It is also not known whether prognostic factors at diagnosis and/or transplantation are relevant for 1- and 2-year survivors of allogeneic transplantation. A recent report on outcomes after transplantation for adults with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) explored prognostic factors likely to be associated with long-term survival for those alive and in remission for at least 1 year after transplantation [13]. In that report, most clinical factors predictive for leukemia-free survival in 1-year survivors were no longer significant 2 or more years after transplantation. For adults with AML, transplantation beyond first remission was the only prognostic factor, and for adults with ALL, extensive chronic GVHD was the only prognostic factor.

Although allogeneic transplantation is routinely offered for children with high-risk AML and ALL, to our knowledge there are no reports that have explored prognostic factors on transplantation outcomes for those who are alive for at least 1 year after their transplantation and are in remission. This information will be useful to counsel patients and their families in regards to realistic expectations regarding leukemia-free (LFS) and overall survival (OS) when they reach the 1-, 2-, 3-, 4-, 5-, and subsequent year landmarks in continuing remission. The data also provide physicians with a heightened awareness of the continued risk for late mortality after transplantation. We used data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) to (1) study risk factors associated with OS and LFS in children and adolescents with AML or ALL who survived without leukemia for at least 1 year after their transplantation and thereafter at various landmark times and (2) develop a personalized prognostic risk score for long-term survival.

MATERIALS AND METHODS

Data Source

The CIBMTR is a voluntary working group of more than 450 transplantation centers that contribute data on consecutive allogeneic and autologous transplantations to the CIBMTR. Compliance and accuracy of data reported to the CIBMTR are monitored by on-site audits. All patients are followed longitudinally annually until death or loss to follow-up. Patients and/or guardian(s) provided written informed consent for data submission and research participation and the study was conducted in accordance with the Declaration of Helsinki. The institutional review board of the National Marrow Donor Program approved this study.

Patients

Patients ages <18 years at transplantation who survived leukemia-free for at least 12 months after transplantation with AML (n = 790) or ALL (n = 1096) were included. These patients constituted the cohort for the 1-year landmark analysis. Cohort members who were alive and leukemia-free at the next landmark were included in analysis of risk factors at that time point. To ensure completeness of follow-up, only centers that submitted 4 or more years of follow-up on more than 80% of their patients who survived for at least 1 year after transplantation were included. Forty-six transplantation centers were excluded for lack of complete follow-up on their patients (n = 256). Patients who received reduced-intensity conditioning regimens were also excluded (<5% of eligible study population), because although the reason for selecting reduced-intensity conditioning was unknown, it was likely to be because of adverse prognostic features, such as poor organ function or severe infection, making these data not generalizable to the rest of the population. Comorbidity data were not collected before 2008. All transplantations were performed between 2000 and 2010. Patients who relapsed within the first year after transplantation or received a second transplantation within the first year and those with Down syndrome or Fanconi anemia were excluded.

Endpoints

Endpoints were LFS and OS at various landmark times from transplantation. Death from any cause was considered an event for OS and treatment failure (inverse of LFS) considered relapse or death as events. Surviving patients were censored at last contact.

Statistical Analysis

Separate analyses were conducted for AML and ALL. Cox proportional hazards models were built to identify risk factors associated with overall mortality and treatment failure (relapse or death) for various landmark times (1, 2, 3, 4, 5, and 6 years from transplantation) [14]. The population at the various landmark time included only patients who were alive and in remission at the landmark times being studied. Variables tested included age at diagnosis, race, performance score, disease status at transplantation, cytogenetic risk, duration of first remission for transplantation in second remission or relapse, conditioning regimen, donor type, history of acute GVHD (within the first year after transplantation), history of chronic GVHD (between transplantation and each landmark time point for each landmark analysis), and transplantation period. Cytogenetic risk was classified as favorable, intermediate, and poor risk as previously reported [15,16]. All variables tested met the assumptions for proportional hazards and those that attained significance of .05 or less were retained in the final model. There were no significant interactions among significant covariates in all models.

A personalized prognostic risk score that could be applied to an individual patient was developed to link their significant risk factor(s) with long-term survival. Scores were assigned based on the ratios of log (hazard ratio) in the final Cox model. Several scoring models were tested and were based on placement of patients with similar risk in the same category on the basis of the fitted Cox model. The scoring models were evaluated by using a Brier score approach, a function that is based on the calculation of the average squared deviation between predicted probabilities and survival [17]. The scoring model that gave the lowest Brier score was picked as the best model. All *P* values are 2 sided. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Study Population

Patient, disease, and transplantation characteristics for AML and ALL are shown separately in Tables 1A and 1B, respectively. The median age at transplantation for patients with AML was 10 years and for ALL, 9 years. Most patients with AML and ALL were Caucasian, reported performance scores of 90 or 100 at transplantation, and were seropositive for cytomegalovirus. Most patients with AML had de novo AML with intermediate-risk cytogenetics and underwent transplantation in first CR. Among the 43 patients with therapy-related AML, 26 patients had history of solid tumor, 15 patients had ALL, and the remaining 2 patients had nonmalignant disease. Most (n = 30) had intermediate-risk cytogenetics and most (n = 36) underwent transplantation in first CR. Most patients with ALL had B cell lineage leukemia and underwent transplantation in second CR. The duration of first CR was less than 36 months for those who underwent transplantation in second CR or relapse. Approximately one-third of patients reported poor-risk cytogenetics, of which almost all were Philadelphia-chromosome positive. Most transplantations for both leukemia types used an unrelated donor and bone marrow was the predominant graft. The predominant conditioning regimen for AML was busulfan with cyclophosphamide and that for ALL was total body irradiation with cyclophosphamide.

Risk Factors Associated with Mortality and Treatment Failure at Various Landmark Times

Table 2A shows risk factors associated with overall mortality and treatment failure at the various landmark times after