Outcome of Allogeneic Stem Cell Transplantation for Patients Transformed to Myelodysplastic Syndrome or Leukemia from Severe Aplastic Anemia: A Report from the MDS Subcommittee of the Chronic Malignancies Working Party and the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation

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Article history:
Received 26 April 2014
Accepted 27 May 2014

Key Words:
Hematopoietic stem cell transplantation
Severe aplastic anemia
Myelodysplastic syndrome
Acute myelogenous leukemia

A B S T R A C T

One hundred and forty patients who had undergone hematopoietic stem cell transplantation (HSCT) for myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) transformation after treatment of severe aplastic anemia (SAA) were identified in the European Group for Blood and Marrow Transplantation (EBMT) database. The median age at HSCT was 29 years (range, 1 to 66 years). The transplant donor was related in 49% cases and unrelated in 51% cases. The 5-year probability of relapse was 17%, and that of nonrelapse mortality was 41%. The 5-year overall survival was 45% ± 9%, better for patients untreated and patients in remission compared with patients with refractory disease. Our data indicate that allogeneic HSCT leads to prolonged survival in close to one-half of the patients transforming to MDS or AML from SAA.

INTRODUCTION

Late clonal complications after immunosuppressive treatment of severe aplastic anemia (SAA) have been well described [1-9]. These include the development of paroxysmal nocturnal hemoglobinuria (PNH) and myelodysplastic syndromes (MDS), as well as the transformation to acute myelogenous leukemia (AML). The incidence of MDS or AML varies among series from 5% up to 20%; a transformation rate of 10% to 15% is most common. These clonal complications may occur at any time after treatment. Risk factors include old age, nonresponse to antithymocyte globulin (ATG), repeat courses of ATG, use of granulocyte colony-stimulating factor (G-CSF) with immunosuppressive treatment and short telomeres. Although several previous studies have investigated the incidence of these late clonal complications, there is little information on outcomes of patients transformed to MDS or AML after treatment of SAA. The largest series, limited to 17 patients, is from a pediatric group [10].

Because PNH is a clonal disease but not a malignant disease, and because the biology and treatment of PNH differ from that of MDS/AML, the present series was limited to patients with MDS or AML who transformed from a previous SAA without having undergone previous hematopoietic stem cell transplantation (HSCT). In this study, we analyzed the outcomes of patients with SAA transformed to MDS or AML and treated by HSCT for disease transformation.

Financial disclosure: See Acknowledgments on page 1450.

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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.05.028

PATIENTS AND METHODS

This study was conducted by the Severe Aplastic Anemia Working Party (SAAWP) and the Chronic Malignancies Working Party (CMWP) of the European Group for Blood and Marrow Transplantation (EBMT). For each transplantation performed, a center reports minimum essential data (MED-A) to a central database. Many centers report a more comprehensive dataset (MED-B) as well. Informed consent was obtained locally according to the regulations applicable at the time of transplantation. Since January 1, 2003, the EBMT has required centers to confirm that written informed consent has been obtained before data acceptance. The study included 140 patients from 77 EBMT centers who underwent transplantation over a 22-year period (1987 to 2009).

Definitions

Patients were retrieved from the database of the CMWP of the EBMT, who were recipients of allogeneic HSCT for MDS/AML with a previous diagnosis of SAA. These patients had received previous immunosuppressive treatment or supportive care. Second HSCTs were not considered.

Outcomes

The outcomes studied were engraftment, defined as time to the first of 3 consecutive days reaching a neutrophil count of 0.5×10^9/L, late graft failure after initial engraftment, incidence of grade II to IV acute graft-versus-host disease (GVHD), and incidence of chronic GVHD, using established criteria for diagnosis of these conditions. Overall survival and relapse incidence were estimated.

Statistical Analysis

The Kaplan-Meier estimator was used for survival, and the cumulative incidence function was used for engraftment, acute GVHD, and chronic GVHD, with death without the event in question serving as the competing risk. Comparisons were done using the log-rank test. A Cox proportional hazards regression model was used with backward covariate elimination, including clinically relevant covariates even if not significantly associated with survival in univariate analysis.

RESULTS

One-hundred and forty patients, including 81 males (58%), were identified in the EBMT database of the CMWP. The median age at time of HSCT was 29 years (range, 1 to 66 years). The median interval from diagnosis of SAA to transformation was 65 months (range, 3 to 214 months), and that from diagnosis of MDS to HSCT was 6 months (range, 2 to 30 months). Of the 140 patients, 104 (74%) were diagnosed with MDS, and 36 (26%) had transformed to AML. MDS was classified as refractory anemia (RA) in 37 cases (26%), refractory anemia with ringed sideroblasts (RARS) in 18 (13%), RAEB/refractory anemia with excess of blasts in transformation (RAEBt) in 7 (5%), chronic myelomonocytic leukemia (CMML) in 4 (3%), and unclassified in 36 (26%). At the time of HSCT, 27 patients (19%) were in any complete remission, 48 (34%) were untreated, 41 (29%) were refractory, and 24 (17%) were other/unclassified. All but 2 of the untreated patients undergoing HSCT were classified as having MDS, but not AML.

Allogeneic HSCT was performed using stem cells from fully matched sibling (n = 56; 40%), mismatched related (n = 12; 9%), or unrelated donors (n = 72; 51%). The stem cell source was bone marrow in 74 cases (53%), peripheral blood in 54 cases (39%), and unrelated cord blood in 12 cases (9%). Conditioning intensity was myeloablative in 110 patients (79%) and reduced-intensity conditioning (RIC) in 30 (21%). Sixty-nine (49%) received total body irradiation, of whom 14 (20%) had received low-dose total body irradiation in the context of RIC. HSCTs were performed between 1987 and 2009 (median, 2002). Median follow-up of surviving patients was 5 years.

Eighteen patients (12%) experienced primary non-engraftment, and 1 patient had late graft failure. The cumulative incidence of acute grade II to IV GVHD was 24% (range, 17% to 32%) by 100 days, and the incidence of chronic GVHD of any degree by 5 years in patients alive at 100 days was 48% (range, 38% to 60%). The probability of relapse at 5 years was 17% (range, 12% to 25%), and nonrelapse mortality was 41% (range, 33% to 50%). Five-year overall survival in this cohort was 45% ± 9% (Figure 1). Survival did not differ significantly by age group (1 to 20, 20 to 40, >40 years), by disease (MDS, AML), by year of transplantation (before 2000, after 2000) (Figure 3; Supplementary Data), by donor (sibling, unrelated, mismatched related), stem cell source used (marrow, peripheral blood, cord blood), or by conditioning intensity (myeloablative, RIC) but was significantly higher in patients who underwent HSCT while in any type of remission (58% ± 20%) or untreated (46% ± 15%) than in patients with refractory disease (24% ± 15%) ($P = .002$ for the comparison of refractory patients against all other disease stages) (Figure 2). Causes of death were infection in 15%, GVHD in 12%, organ toxicity in 31%, and graft failure in 4% of the reported deaths.

DISCUSSION

The present series is a series of patients with SAA who had transformed to MDS or AML and subsequently underwent allogeneic HSCT for transformed disease. Transformation of SAA to MDS or AML is well described and occurs in approximately 5% to 20% of patients receiving immunosuppressive treatment. Whether this transformation is a consequence of treatment and/or of the original disease has not yet been determined and is of minor importance for the present analysis. Because these are rare events, this present series was accumulated over 22 years and involved numerous transplantation centers. The main findings are (1) 45% of patients became long term survivors; (2) treatment-related mortality was considerable; and (3) the only factor significantly associated with outcome was disease stage before HSCT, with untreated patients and patients in any type of remission doing better than patients with refractory disease. This was the sole factor significantly associated with survival in both univariate and multivariate analyses; thus, details of the multivariate analysis are not shown. Obviously, selecting patients who have received chemotherapy without responding would result in a negatively selected cohort bound to have unfavorable outcomes.

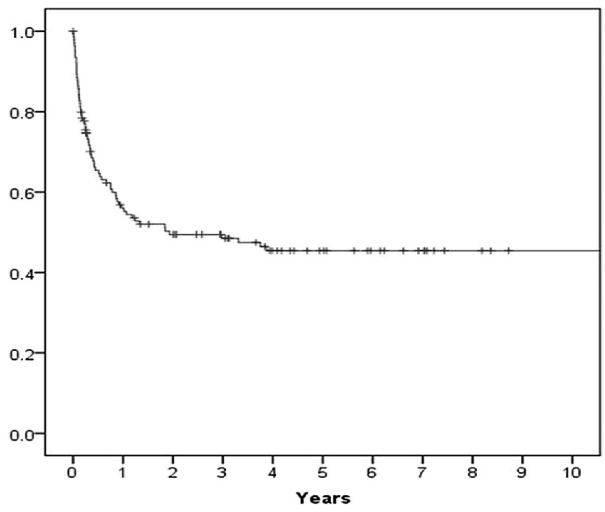

Figure 1. Survival of the 140 patients undergoing allogeneic HSCT for MDS/AML transformed from SAA.

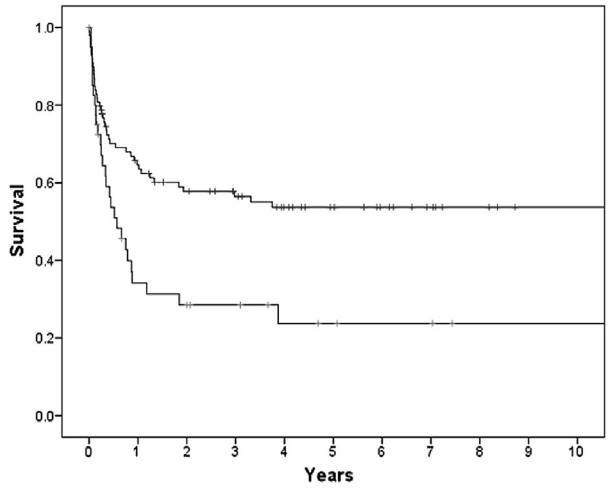

Figure 2. Survival of patients undergoing HSCT with refractory disease compared with those undergoing HSCT while in any type of remission or with untreated disease ($P = .002$).

Of note, the majority of donors used were unrelated. This is not surprising, especially in younger patients, given that those at risk of developing secondary MDS after treatment of SAA would have most commonly received a sibling donor graft at the time of diagnosis of SAA, had there been a good donor available.

The 17% relapse rate for our cohort appears to be lower than that for similar cohorts of patients undergoing transplantation for MDS not associated with SAA. Whether this reflects the fundamental biology of this disease or is related to the rather young age of patients with SAA that transforms to MDS/AML cannot be answered by our data. The rate of nonrelapse mortality is considerable and needs to be lowered. There was a high proportion of deaths related to toxicity (23 of 71 deaths; 32%), most likely explained by the use of intensive conditioning in patients with many previous transfusions and possibly iron overload. Another possible explanation for increased toxicity is that the original bone marrow failure for which the patient had been treated was part of an inherited but unrecognized marrow failure syndrome, such as a telomeropathy or Fanconi anemia, making the patient more prone to conditioning-related toxicity. These possibilities should be carefully excluded before the initiation of conditioning, even in adult patients [11].

Our graft failure rate of 12% is rather high, considering that a large majority of the patients received myeloablative conditioning. This high rate of failure might be attributable to previous transfusions in many patients, leading to alloimmunization. Although we lack data on the number of transfusions received or the presence of pretransplantation anti-HLA antibodies, the median disease duration of more than 65 months before transformation to MDS/AML indicates that most patients most likely received multiple transfusions. Only 4% of deaths were attributed to nonengraftment, possibly related to autologous recovery or rescue treatment.

Owing to this study's retrospective nature, data on this is lacking, and these and other factors such as patient age and comorbidities need careful evaluation before choosing a myeloablative or RIC regimen for a given patient. The use of RIC regimens was not associated with better survival; however, we lack knowledge on how patients were selected for one or the other type of regimen.

This study has other limitations as well. We do not have detailed knowledge of the pretransplantation treatment of SAA for the majority of patients; however, we do know that none had undergone previous HSCT. This series spans 22 years, and many factors affecting transplantation outcomes have changed over the years; however, year of HSCT did not affect survival in this series. Our study also lacks data on how many patients received pretransplantation chemotherapy, with the inherent risk of failure to recover hematologic counts after chemotherapy on a background of previous SAA. Finally, patients, types of transformed disease, and treatment strategies were quite heterogeneous. Nevertheless, we report that of 140 patients undergoing allogeneic HSCT for MDS/AML transformed from SAA, 45% were rescued long term.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: A.A.H. and C.M.H. designed the study and wrote the manuscript. J.R.P. performed the statistical analyses and wrote the manuscript. G.S., A.T., P.A.B., M.N.P.M.S., R.F., A.G., C.D., A.B., A.L., M.A., C.P., M.R., A.A.B., L.V., T.W., J.M., and N.K. wrote and approved the manuscript.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2014.05.028.

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