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Clinical Research: Supportive Care

Improved Treatment-Related Mortality and Overall Survival of Patients with Grade IV Acute GVHD in the Modern Years

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A B S T R A C T

The impact of advances in supportive care and hematopoietic stem cell transplantation (HSCT) practices on the outcomes of patients who develop grade III or IV acute graft-versus-host disease (GVHD) is unknown. We performed a retrospective analysis of 427 patients with overall grade III or IV acute GVHD treated at 2 partner institutions between 1997 and 2012. We compared treatment-related mortality (TRM) and overall survival (OS) in 2 cohorts based on the year of transplantation, 1997 to 2006 (n = 222) and 2007 to 2012 (n = 205), using multivariate analysis, adjusting for significant patient-, disease-, and transplantation-related factors. Recipient age, reduced-intensity conditioning, unrelated donor, and peripheral blood stem cell grafts in the patients with grade III or IV acute GVHD increased over time. In the unadjusted analysis, 12-month OS increased over time (30% in 1997 to 2006 versus 42% in 2007 to 2012; $P = .003$) reflecting a decrease in TRM (58% in 1997 to 2006 versus 38% in 2007 to 2012; $P = .0002$), and an increase in PFS (29% in 1997 to 2006 versus 43% in 2007 to 2012; $P = .002$). On multivariate analysis, the period of transplantation remained a significant predictor for OS (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.54 to 0.94; $P = .02$), progression-free survival (PFS) (HR, 0.70; 95% CI, 0.52 to 0.94; $P = .02$), and TRM (HR, 0.57; 95% CI, 0.39 to 0.82; $P = .002$). In subgroup analysis, these differences were observed mainly in patients with grade IV acute GVHD. The outcomes of patients who develop overall grade III or IV acute GVHD after allogeneic HSCT has improved over time, with lower TRM and improved OS. This improvement in outcomes was seen primarily in patients with grade IV acute GVHD.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) offers a potentially curative therapy for many patients with hematologic malignancies and nonmalignant hematologic diseases [1,2]. Despite significant progress in the field of allogeneic HSCT over the past 2 decades, acute graft-versus-host disease (GVHD) remains a major contributor to post-transplantation treatment-related mortality (TRM) [3,4]. Acute GVHD affects approximately 10% to 50% of HSCT recipients even with the use of standard prophylactic immunosuppressive regimens [4,5]; thus, acute GVHD remains an important post-transplantation complication, leading to high morbidity and mortality in allogeneic HSCT recipients.

Several factors contribute to the risk and severity of acute GVHD, including degree of donor–recipient HLA matching, intensity of conditioning regimen, older age, previous donor alloimmunization, and GVHD prophylactic regimen [6]. Historical studies reported an overall long-term survival of 10% to 25% in patients with severe acute GVHD, defined as overall grade III or IV disease [7-12]. Since then, however, significant changes in allogeneic HSCT practice have included the introduction of peripheral blood, cord blood, and haploidentical transplantation; the advent of reduced-intensity conditioning regimens; an increasing age of transplant

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recipients; and an expanding spectrum of diagnoses for which HSCT is indicated. In addition, certain advances in the field of allogeneic HSCT have clearly led to a reduction in TRM and improved transplantation outcomes [2,13], including more accurate HLA matching of unrelated donors, better prevention and treatment of infectious complications, improved supportive care measures, and advances in other related fields, such as critical care medicine, transfusion medicine, and nephrology [2,13-20]. Consequently, the overall prognosis for today's patients who develop severe acute GVHD is unclear [21,22].

A better understanding of how the advances in allogeneic HSCT have affected the outcomes of patients with severe acute GVHD is instrumental for comparing the efficacy of novel therapies to a more appropriate historical control in the modern years, and also for informing our ability to provide more accurate prognostic information for this patient population. Therefore, we conducted a retrospective analysis examining changes in TRM, progression free-survival (PFS), and overall survival (OS) of patients who underwent allogeneic HSCT and subsequently developed overall grade III or IV acute GVHD between 1997 and 2012. We hypothesized that patients developing acute GVHD in the most recent years would have lower TRM and improved OS compared with those patients from the earlier time period.

METHODS

Study Design

We conducted a retrospective analysis of all adult patients (age ≥18 years) who underwent allogeneic HSCT and subsequently developed overall grade III or IV acute GVHD at the Dana-Farber Cancer Institute and Massachusetts General Hospital between 1997 and 2012. We initially categorized patients into three 5- to 6-year consecutive cohorts based on the date of HSCT (1997 to 2001, 2002 to 2006, and 2007 to 2012). We noted similar outcomes in the 1997 to 2001 and 2002 to 2006 cohorts, and thus combined those 2 cohorts into a single cohort and compared patients with acute GVHD who underwent HSCT in 1997 to 2006 (earlier cohort) with those who did so in 2007 to 2012 (more recent cohort). We defined overall grade III and IV acute GVHD based on clinician assessment using previously described consensus criteria with the modified Glucksberg grading system [23]. The clinicians used the same grading system throughout the 2 different time periods of this analysis. The acute GVHD grading incorporated patients' performance status specifically related to acute GVHD. The research team reviewed the electronic medical record to confirm and ensure use of the same criteria to grade acute GVHD for all study participants.

Patients were included in this analysis regardless of conditioning regimen intensity, donor type (matched related, matched unrelated, mismatched related or unrelated, haploidentical, or umbilical cord blood), donor source (bone marrow, peripheral blood stem cells, or umbilical cord blood), or GVHD prophylaxis regimen. Patients with both classical acute and delayed-onset acute GVHD were included. To accurately assess GVHD outcomes, patients who relapsed and subsequently developed acute GVHD were excluded. Patients who initially presented with grade III acute GVHD and then subsequently developed grade IV acute GVHD were included in the analyses. This study was approved by the Institutional Review Board of the Dana-Farber/Harvard Cancer Center.

We identified the eligible cohort using the Dana-Farber Cancer Institute and Massachusetts General Hospital transplantation databases. We then conducted a comprehensive medical record review to confirm the diagnosis of grade III or IV acute GVHD; to obtain additional information about patient clinical characteristics, including comorbidities (at the time of onset of grade III or IV acute GVHD), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (at the time of onset of grade III-IV acute GVHD), GVHD prophylaxis and treatment regimens, and underlying diagnosis and disease status at the time of HSCT; and to obtain information on transplantation-related variables, including conditioning intensity, donor type, donor source, donor age, and donor–recipient sex match.

Study Endpoints

The primary study endpoint was TRM, defined as death due to any cause occurring after HSCT without documented underlying disease relapse. Secondary outcomes included PFS and OS. PFS was defined as the time from the date of development of grade III or IV acute GVHD until the date of underlying disease relapse or death, whichever occurred first. OS was defined as the time from the date of development of grade III or IV acute GVHD until the date of death from any cause. PFS and OS for patients with grade III acute GVHD was measured from the time of development of grade III acute GVHD. Similarly, PFS and OS for patients with grade IV acute GVHD was measured from the time of development of grade IV acute GVHD. Patients who were alive at the time of our analysis were censored at the date last known to be alive.

We determined the patients' causes of death through a comprehensive chart review. We categorized cause of death as underlying disease, GVHD without disease relapse, infection without active GVHD, or other.

Statistical Analysis

The study patients were divided into 2 cohorts based on the timing of HSCT: 1997 to 2006 and 2007 to 2012. Categorical or continuous characteristics were compared in the 2 cohorts using the chi-squared test or Wilcoxon rank-sum test. PFS and OS were estimated using the Kaplan-Meier method. The log-rank test was used to compare PFS and OS between groups, and Cox proportional hazards regression models were used to study the time effects on PFS and OS while adjusting for other risk factors. Time to TRM was analyzed using relapse/death from disease as competing risks. In competing-risk settings, Gray's method was used for comparisons between groups, and competing-risk regression was used to test the significance of time effects, adjusting for other covariates. Other factors adjusted for in the regression setting included patient age, ECOG PS, comorbidities (cardiac and renal), disease diagnosis, disease status at the time of HSCT, conditioning regimen intensity, stem cell source, GVHD prophylaxis regimen, donor–recipient sex match, donor HLA-matching, donor age, grade of acute GVHD, time to onset of acute GVHD, and bacterial, fungal, and viral infections. All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient-, Disease-, and Transplantation-Related Characteristics

The study population comprised 427 patients diagnosed with severe acute GVHD in the 2 cohorts, 1997 to 2006 (n = 222) and 2007 to 2012 (n = 205). Table 1 presents patient-, disease-, and transplantation-related characteristics by cohort. The median age of HSCT recipients increased over time (45 years in 1997 to 2006 versus 52 years in 2007 to 2012; $P < .0001$), as did the proportions of patients receiving reduced-intensity conditioning and receiving peripheral blood stem cell grafts. The median time to onset of acute GVHD increased from 26.5 days in the earlier cohort to 40 days in the more recent cohort ($P < .0001$). There were differences in the spectrum of underlying diagnoses across time, with a decline in the number of patients with myeloproliferative neoplasm (MPN) and chronic myelogenous leukemia (CML) and an increase in the number of patients with acute leukemia and myelodysplastic syndrome (MDS) in the more recent cohort. There were no significant differences in donor age and donor–recipient sex match between the 2 cohorts, although there was a decline in the proportion of HSCTs using matched related donors in the more recent cohort. Among all of the patients with severe acute GVHD, the proportion of patients with grade III acute GVHD increased over time from 47% in the earlier cohort to 63% in the more recent cohort, whereas the proportion of patients with grade IV acute GVHD declined in the more recent cohort. In patients with grade III acute GVHD, gastrointestinal involvement increased from 47% in the earlier cohort to 67% in the more recent cohort. In patients with grade IV acute GVHD, stage 4 skin involvement increased from 33% in the earlier cohort to 54% in the more recent cohort. No other between-cohort differences in organ involvement in patients with grade III and IV acute GVHD were seen. Patients in the earlier cohort were more likely to undergo HSCT with relapsed refractory disease.

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