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Late Acute and Chronic Graft-versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Several distinct graft-versus-host disease (GVHD)-related syndromes have been defined by the National Institutes of Health Consensus Conference. We enrolled a prospective cohort of 911 hematopoietic cell transplantation (HCT) recipients at 13 centers between March 2011 and May 2014 to evaluate 4 GVHD syndromes: late acute GVHD (aGVHD), chronic GVHD (cGVHD), bronchiolitis obliterans syndrome, and cutaneous sclerosis. The median age at HCT was 53.7 years. The majority of patients received a peripheral blood stem cell transplant (81%) following nonmyeloablative or reduced-intensity conditioning (55%). Pediatric age group and use of bone marrow and umbilical cord blood grafts were underrepresented in our cohort ($\leq$11%). The cumulative incidence of late aGVHD (late onset and recurrent) was 10% at a median of 5.5 months post-HCT, that of cGVHD was 47% at a median of 7.4 months, that of bronchiolitis obliterans was 3% at a median of 12.2 months, and that of cutaneous sclerosis was 8% at a median onset of 14.0 months. Late aGVHD and bronchiolitis obliterans had particularly high nonrelapse mortality of 23% and 32%, respectively, by 2 years after diagnosis. The probability of late aGVHD- and cGVHD-free, relapse-free survival was 38% at 1 year post-HCT and 26% at 2 years post-HCT. This multicenter prospective study confirms the high rate of late aGVHD and cGVHD syndromes and supports the need for continuous close monitoring and development of more effective GVHD treatment strategies to improve HCT success.

INTRODUCTION

Chronic graft-versus host disease (cGVHD) is one of the leading causes of late mortality and morbidity after allogeneic hematopoietic cell transplantation (HCT) [1,2]. The clinical presentation of late acute GVHD (aGVHD) and cGVHD is heterogeneous, with several distinct syndromes as defined by the National Institutes of Health (NIH) Consensus Conference in 2005 [3] and confirmed in its 2014 update [4]. The Chronic GVHD Consortium enrolled allogeneic HCT recipients in a prospective multicenter, longitudinal observational cohort study and followed them closely for the development of 4 GVHD syndromes: late aGVHD, bronchiolitis obliterans syndrome, cutaneous sclerosis, and cGVHD. Although bronchiolitis obliterans and cutaneous sclerosis are

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considered part of the cGVHD syndrome, they are also reported separately because they are of particular interest owing to their unique clinical manifestations and poor response to available therapies.

Because a goal of the present study was to develop a biorepository of biological material for future studies, research samples were collected at enrollment and during the first year. Detailed clinical evaluations were performed, and additional research samples were collected when GVHD syndromes developed. This report focuses on the incidence, clinical manifestations, and outcomes of the 4 syndromes evaluated in this cohort. This information is important for future biomarker studies and for understanding the clinical features of these syndromes, especially given that a growing number of novel therapeutic interventions are now available for testing as GVHD prophylaxis agents, as well as for the treatment of GVHD once the diagnosis is established.

METHODS

Study Design

The Chronic GVHD Consortium includes 13 centers that enrolled a total of 911 allogeneic HCT recipients over a 3-year period (March 2011 to May 2014), and followed them prospectively. Enrollment was allowed up to 4 months post-HCT (121 days), as long as the patient did not developed late aGVHD or cGVHD. A total of 413 patients were enrolled before HCT, and 498 patients were enrolled after HCT. The median time to enrollment was 1.9 months (interquartile range, −0.6 to 2.8 months). All sites obtained Institutional Review Board approval for the study, and all participants provided written informed consent.

The late aGVHD and cGVHD syndromes were defined according to the NIH consensus criteria [3]. In patients who did not develop a GVHD syndrome, research samples were collected at 2 time points (day +100 and either day +180 or day +365). If a late GVHD syndrome developed, samples were collected at onset and either 3 or 6 months later. Supplemental Table S1 provides details on the number of samples available for each late GVHD syndrome, and access to these samples is available on request from the authors.

Statistical Analysis

The cumulative incidence for each syndrome was calculated, treating recurrent malignancy/progression or death as competing risks [5]. For analysis of late aGVHD, onset of cGVHD was also considered a competing risk because by definition, late aGVHD cannot be diagnosed once cGVHD is diagnosed. Overall survival was calculated using Kaplan-Meier estimates, and 95% confidence intervals (CIs) were calculated using the variance derived from the formula of Greenwood [6].

Late aGVHD- and cGVHD-free, relapse-free survival was calculated, because patients who did not develop any late aGVHD or cGVHD-related syndrome and survived without recurrent malignancy or progression represent the most successful outcome of HCT. In this composite endpoint, death, recurrent or progressive underlying malignancy, and development of late aGVHD or any cGVHD syndrome were considered events. A second analysis evaluated the same endpoint but also considered grade III-IV classic aGVHD as an event [7].

Multivariate analyses were performed using stepwise forward selection. A P value $\leq .05$ was the criterion for inclusion in the final models [8]. The potential variables were recipient age at HCT, patient sex, donor–recipient sex mismatch, race, diagnosis, disease status at HCT, center location, use of total body irradiation (TBI) in the conditioning regimen, conditioning regimen intensity, recipient/donor CMV status, previous aGVHD, donor type, graft type, and Karnofsky performance status (KPS).

RESULTS

This analysis included 911 allogeneic HCT recipients. Patient and transplant characteristics are described in Table 1. The median recipient age at HCT was 53.7 years (range, 19-77.9 years). One-third underwent HCT from an HLA-identical sibling donor, 44% from an HLA-matched unrelated donor (URD), and 20% from an HLA-mismatched URD, which includes umbilical cord blood (UCB). Transplants from HLA-mismatched related (<1%) and haploidentical donors (2%) were rare. Most patients received a peripheral blood stem cell (PBSC) graft (81%), and fewer received a UCB (11%) or bone marrow (8%) graft. Slightly less than one-half (45%) received myeloablative conditioning. The majority (65%) of recipients were treated for acute leukemia or myelodysplastic syndrome (MDS), and 88% had early or intermediate disease status. In 21% of cases, the donor was a female and the recipient a male. The median follow-up of survivors was 26.3 months (interquartile range, 20-35.3 months).

Table 1
Demographic Data (n = 911)

Characteristic	Value
Recipient age at HCT, yr, median (range)	53.7 (19-77.9)
11-30, n (%)	95 (11)
31-50, n (%)	268 (29)
>50, n (%)	548 (60)
Donor type (n = 898), n (%)	
HLA identical sibling	297 (33)
HLA-matched other relative	8 (1)
HLA-matched unrelated donor	393 (44)
HLA-mismatched relative (single antigen/allele-mismatched)	3 (<1)
HLA-mismatched unrelated donor	181 (20)
Haploidentical relative (2 or more antigen/allele-mismatched)	16 (2)
Graft type (n = 910), n (%)	
Bone marrow	77 (8)
Umbilical cord blood	102 (11)
Peripheral blood stem cells	731 (81)
Conditioning regimen intensity (n = 910), n (%)	
Myeloablative	405 (45)
Nonmyeloablative	505 (55)
Total body irradiation, n (%)	
Yes	408 (45)
No	503 (55)
Graft-versus-host disease prophylaxis, n (%)*	
Calcineurin inhibitor + methotrexate with or without other	390 (43)
Calcineurin inhibitor + mycophenolate mofetil	225 (25)
Calcineurin inhibitor + sirolimus	97 (11)
Calcineurin inhibitor + mycophenolate mofetil + sirolimus	64 (7)
Antithymoctye globulin/T cell depletion with or without other	23 (3)
Other	112 (12)
Center location, n (%)	
Pacific/Mountain	279 (31)
Central	260 (28)
Eastern	372 (41)
Donor–recipient sex match (n = 896), n (%)	
Female to male	190 (21)
Other	708 (79)
Time from HCT to study consent, mo, median (range)	1.9 (−5.5 to 4.0)
Follow-up of survivors, mo, median (range)	26.3 (5.1-53.8)

* Total >100% because of rounding.

Because enrollment was allowed up to 4 months post-HCT, we performed a sensitivity analysis limited to the 413 patients who were enrolled pre-HCT, to evaluate the cumulative incidence of each syndrome. The estimates were compared with those for the 498 patients enrolled post-HCT. Because the 2 estimates were similar (data not shown), suggesting that the population enrolled post-HCT was not unduly biased by early death, relapse, or development of late aGVHD, we report estimates for the entire cohort in this analysis.

Late aGVHD

By 2 years post-HCT, recurrent or late-onset aGVHD developed in 10% (95% CI, 8%-12%) of HCT recipients (Table 2 and Figure 1, A). The median time to onset was 5.5 months