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Risk Factors and Outcome of Chronic Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation—Results from a Single-Center Observational Study

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A B S T R A C T

Chronic graft versus host disease (cGVHD) is the most frequent long-term complication after allogeneic stem cell transplantation (allo-SCT) and results in impaired quality of life and increased long-term morbidity and mortality. We analyzed 243 patients with cGVHD, documented according to the 2005 revised National Institutes of Health consensus criteria, to identify risk factors for the occurrence of cGVHD and outcomes for the patients with cGVHD. Patients without evidence of cGVHD (n = 147) were used as controls. Performing univariate and multivariate Cox regression analyses, we identified prior acute GVHD grades III or IV (hazard ratio [HR], 2.01; $P = .005$), use of peripheral blood stem cell graft (HR, 2.10; $P = .03$), and HLA-mismatched allo-SCT from unrelated donor (HR, 1.57; $P = .02$) as independent risk factors for cGVHD. Performing Kaplan-Meier analyses, progressive compared with de novo and quiescent onset of cGVHD and a platelet count of less than 100/nL compared with more than 100/nL at the time of cGVHD onset were associated with a significantly increased cumulative incidence of transplantation-related mortality (TRM) and significantly decreased overall survival. Furthermore, we found a significantly higher incidence of TRM in patients with severe cGVHD compared with patients without cGVHD (58% versus 11%, $P < .0001$). However, in subgroup analysis, patients with severe cGVHD and involvement of the lung, liver, or gastrointestinal (GI) tract had a 6.5-fold significantly higher incidence of TRM (72%), whereas patients with severe cGVHD lacking lung, liver, or GI involvement had only a 2.8-fold significantly higher incidence of TRM (31%) compared with patients without cGVHD (11%; $P < .0001$ and $P = .03$). Patients without lung, liver, or GI involvement did not have a significantly different TRM compared with patients with moderate cGVHD (31% versus 25%, $P = .52$). In conclusion, we confirm prior known risk factors for the occurrence of cGVHD and subsequent mortality and we provide evidence that the presence of lung, liver, or GI involvement in patients with severe cGVHD defines a subgroup with high mortality after allo-SCT; however, in the absence of these risk factors, the outcome appears not to be impaired compared with moderate cGVHD.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is 1 of the most common late complications after allogeneic stem cell transplantation (allo-SCT) [1,2]. Although improvements have been made to reduce the incidence of early transplantation-related complications such as acute graft-versus-host disease (aGVHD), there has been little progress in preventing cGVHD, which occurs in 30% to 70% of patients [3,4]. Clinical manifestations of cGVHD are heterogeneous in terms of onset, involved organ sites, and severity, resulting in impaired quality of life and increased long-term morbidity and mortality [4,5]. The main causes for morbidity and mortality are cGVHD-associated immunodeficiency, organ dysfunction, and prolonged immunosuppression induced by treatment. In the past, any manifestation of GVHD that was present or occurred at 100 days after allo-SCT or thereafter was defined as cGVHD, regardless of clinical features. In 2005, the National Institutes of Health (NIH) Consensus Conference established diagnostic criteria of cGVHD that are based on clinical manifestations independent of the time after allo-SCT and a global severity score for cGVHD (mild, moderate and severe) has been proposed [5]. In recent years, several studies analyzed various risk factors for cGVHD and the most consistently reported risk factors are prior aGVHD [2,6-18], use of peripheral blood stem cell (PBSC) grafts [7,18-24], female donors in male recipients [2,7,9,14,15,17,18,25,26], HLA

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mismatch, the use of unrelated donors (URD) [2,7,10,27], and older patient age [2,6-9,11,13-15,25]. However most of the studies did not apply the NIH diagnostic criteria of cGVHD. Therefore, we aimed to identify risk factors for the occurrence of cGVHD and analyze the outcomes of patients with cGVHD at our transplantation center, applying the 2005 revised NIH consensus criteria [5].

MATERIAL AND METHODS

Patients

A total of 390 patients and their donors were included in the retrospective observational study. The individuals underwent allo-SCT between 1999 and 2013 at the University Hospital of Regensburg and were enrolled in a clinical investigation approved by the institutional research ethics committee after providing informed consent. Conditioning and prophylactic immunosuppression were performed according to standard protocols. Standard conditioning regimens consisted of 8 Gy to 12 Gy fractionated total-body irradiation (TBI) followed by high-dose cyclophosphamide or classic busulfan/cyclophosphamide. Reduced-intensity conditioning consisted mainly of fludarabine/BCNU and melphalan regimens [28,29]. Patients receiving allo-SCT from URD underwent in vivo T cell depletion with antithymocyte globulin (ATG) in the context of pretransplantation conditioning [30].

Among the analyzed individuals were 243 patients with cGVHD, according to the 2005 revised NIH consensus criteria [5]. Patients without evidence of cGVHD (n = 147) were used as controls. Three hundred sixteen patients who underwent transplantation throughout the same period were excluded from the analysis after applying predefined criteria: received cord blood as stem cell source, haploidentical allo-SCT, death due to aGVHD, death before day 100, relapse before day 100, or more than 1 allo-SCT. Altogether, the incidence of cGVHD in all patients (included and excluded) was 55%.

In patients who underwent transplantation before 2006 (n = 158), cGVHD grading according to the 2005 revised NIH consensus criteria was performed retrospectively by reviewing individual medical records, which were consistently updated by transplantation-experienced medical specialists, after allo-SCT and documented all relevant information required to perform accurate classification and grading of organ involvement. cGVHD was diagnosed if there was presence of at least 1 diagnostic clinical sign of cGVHD or presence of at least 1 distinctive manifestation confirmed by biopsy or other relevant tests. Patients with late aGVHD, which includes persistent, recurrent, or delayed-onset aGVHD without diagnostic or distinctive signs of cGVHD, were evaluated as patients without cGVHD [31]. Starting in 2006, NIH cGVHD grading was performed in all subsequent patients (n = 232). Because cGVHD grading was consistently performed (mainly prospectively) according to the 2005 revised NIH consensus criteria, we did not apply the recently published 2014 revised NIH consensus criteria [3] in our study. To compare our results with results obtained from analyses based on the historical cGVHD grading, we reclassified the cohort of cGVHD patients according to the historical cGVHD criteria [32] and identified limited cGVHD in 37 (15%) and extensive in 206 (85%) patients.

Individuals were of Caucasian ethnic background only. Analyzed patient, donor, and transplantation related risk factors included recipient gender and age, donor age, donor-recipient cytomegalovirus (CMV) serostatus, donor-recipient gender combination, donor relation, HLA compatibility of URD and sibling donor, disease stage at allo-SCT, intensity of conditioning regimen, application of TBI, stem cell source, ABO blood group compatibility, donor lymphocyte infusion (DLI), and grade of aGVHD before onset of cGVHD. One hundred six patients received DLI either preemptively to decrease relapse in patients with increased risk of relapse or with decreasing donor chimerism or used as salvage therapy in patients with obvious relapse. Twenty-seven patients died shortly after DLI because of relapse. The remaining 79 patients were included in the risk factor analysis for subsequent cGVHD. Patient characteristics are shown in Table 1. There were no significant differences between patients with and without cGVHD in terms of clinical features, except stem cell source and prior aGVHD.

Table 1
Patients and Clinical Characteristics

Characteristic	No cGVHD	cGVHD	*P* Value
No. of patients	147	243	
Disease			
ALL	12 (8)	23 (10)	
AML	56 (38)	100 (41)	
CLL	3 (2)	11 (5)	
CML	12 (8)	19 (8)	
Hodgkin	2 (2)	6 (2)	
MDS	9 (6)	13 (5)	
MM	18 (12)	26 (11)	
MPS	5 (3)	3 (1)	
NHL	20 (14)	29 (12)	
OMF	4 (3)	10 (4)	
Others*	6 (4)	3 (1)	
Gender			.29
Male	82 (56)	150 (62)	
Female	65 (44)	93 (38)	
Age, mean (range), yr	48 (17-71)	48 (16-69)	.83
Stem cell source			***.03***
Bone marrow	24 (16)	21 (9)	
Peripheral blood	123 (84)	222 (91)	
Conditioning			.30
Standard	48 (33)	67 (28)	
RIC	99 (67)	176 (72)	
TBI application			.37
No TBI	97 (66)	171 (70)	
TBI	50 (34)	72 (30)	
Donor type			.22
Unrelated	101 (69)	151 (62)	
Sibling	46 (31)	92 (38)	
Disease stage			1.0
Early/intermediate	98 (67)	161 (66)	
Advanced	49 (33)	82 (34)	
DLI			.06
No DLI	99 (67)	185 (76)	
DLI	48 (33)	58 (24)	
aGVHD			***.01***
Grade 0-II	144 (95)	212 (87)	
Grade III-IV	7 (5)	31 (13)	

Data presented are n (%), unless otherwise indicated.
ALL indicates acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPS, myeloproliferative syndrome; NHL, non Hodgkin's lymphoma; OMF, osteomyelofibrosis; RIC, reduced-intensity conditioning.
Bold italics denotes statistically significant *P* values.
* Others: 6 severe aplastic anemia, 2 paroxysmal nocturnal hemoglobinuria, 1 Ewing sarcoma.

Definitions

Transplantation-related mortality (TRM) was defined as death unrelated to relapse or disease progression, *overall survival* (OS) was defined as time from allo-SCT until death from any cause, and *relapse* was defined as occurrence of disease after achieving remission. The type of cGVHD onset was defined as follows: (1) *de novo*, when cGVHD occurred without preexisting aGVHD, (2) *quiescent*, when cGVHD occurred after resolution of prior aGVHD and completion of its therapy, or (3) *progressive*, when cGVHD occurred before resolution of prior aGVHD and completion of its therapy (ongoing prednisone therapy with at least .5 mg/kg body weight). To determine the association between overall severity of cGVHD and the incidence of TRM, OS, and relapse, we used the maximum severity and not severity at onset of cGVHD.

Statistical Analysis

Cox regression was used to identify risk factors for cGVHD. First univariate Cox regression analysis was performed and factors with a *P* value less than .05 indicating an association with cGVHD were entered in a multivariate analysis. Risk factors with a *P* value less than .05 were considered to be statistically significant. The cumulative incidences of TRM, relapse, and OS after allo-SCT were calculated by the Kaplan-Meier method. Differences in terms of clinical features between individuals with and without cGVHD were calculated by chi-square test. In cases where the expected values in any of the cells of the contingency table were below 5, Fisher exact test was used instead of chi-square test. Because the character of the study was a retrospective exploratory study, we did not adjust for multiple testing [33].

RESULTS

Characteristics of cGVHD

Two hundred forty-three patients with cGVHD according to the 2005 revised NIH consensus criteria [5] were analyzed in this study. The median time from transplantation to onset of cGVHD was 219 days (range, 63 to 2632) (Table 2). The type of cGVHD onset was de novo in 76 (31%),