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

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A B S T R A C T

There are little data regarding the incidence, clinical manifestations, risk factors, and outcomes of late acute graft-versus-host disease (aGVHD). We evaluated patients with late aGVHD after allogeneic hematopoietic cell transplantation (HCT) between 2007 and 2012 and compared their outcomes to patients with early-onset aGVHD. Of the 511 allogeneic HCT recipients, 75 developed late aGVHD (cumulative incidence: 14.7% (95% confidence interval [CI], 11.6% to 17.8%) versus 248 with early-onset aGVHD (cumulative incidence: 49% [95% CI, 45% to 53%]). Among those with late aGVHD, 52% had persistent, 39% had recurrent, and 9% had de novo late aGVHD. Advanced (grades III and IV) early-onset aGVHD was associated with a higher risk of developing late aGVHD (hazard ratio [HR], 1.9; 95% CI, 1.2 to 3.1; $P = .01$). Forty-eight percent (95% CI, 36% to 60%) of late aGVHD versus only 31% (95% CI, 26% to 37%) of early-onset aGVHD progressed to chronic GVHD by 2 years. Higher proportion of persistent (53%) as compared to recurrent (39%) and de novo (46%) late aGVHD progressed to cGVHD at 2 years. The overall survival was 59% (95% CI, 49% to 72%) in late aGVHD and 50% (95% CI, 44% to 57%) in early-onset aGVHD. Persistent late aGVHD had worse overall survival and nonrelapse mortality (45% and 39%, respectively) than recurrent (74% and 18%, respectively) and de novo (83% and 0%, respectively) late aGVHD. Compared with HLA-identical sibling HCT, unrelated donor transplantations were associated with a higher risk of mortality in patients developing late aGVHD (HR, 6.1; 95% CI, 2.3 to 16.2; $P < .01$). In a landmark analysis (evaluating 100-day survivors among early-onset aGVHD), no difference was seen in late mortality (after 100 days) between early-onset and late aGVHD (HR, .96; 95% CI, .59 to 1.55; $P = .85$); however, the risk of cGVHD was nearly doubled (HR, 1.81; 95% CI, 1.16 to 2.82; $P = .01$) in patients with late aGVHD. Late aGVHD is a relatively common complication after allogeneic HCT. Poorer outcomes in those with persistent late aGVHD imply need for more effective therapy in this group to improve transplantation outcomes. A higher risk of subsequent chronic GVHD needs further evaluation and close monitoring.

INTRODUCTION

Late acute graft-versus-host disease (aGVHD) is defined as presence of symptoms and signs of aGVHD more than 100 days after allogeneic hematopoietic stem cell transplantation (HCT) [1]. Several retrospective studies have evaluated reclassification of patients with chronic graft-versus-host disease (cGVHD) into late aGVHD, classic cGVHD, and overlap syndrome, and they have reported conflicting outcomes in those with late aGVHD [2-4]. Insufficient data are available regarding onset, clinical presentation, response to treatment, and major outcomes of late aGVHD.

We evaluated a retrospective cohort of patients with late aGVHD among adult allogeneic HCT recipients who underwent an HCT at the University of Minnesota between January 1, 2007 and December 31, 2012.

The main objectives of this study were to evaluate the outcomes for those with late aGVHD, compared with those for patients with early-onset aGVHD. Secondary objectives included identifying risk factors for onset of late aGVHD and risk factors for nonrelapse mortality (NRM) in patients with late aGVHD.

PATIENTS AND METHODS

Data of all consecutive adult patients who underwent an allogeneic HCT between January 1, 2007 and December 31, 2012 (n = 511) and who were reported to have GVHD (acute and/or chronic) and were included in the

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University of Minnesota bone marrow transplantation database were retrospectively reviewed to identify patients with late aGVHD. Five patients were reclassified from having cGVHD to having late aGVHD. Overall, 75 patients with late aGVHD and 248 with early-onset aGVHD were included in this study. All patients signed informed consent before their HCT and this retrospective analysis was approved by the institutional review board at the University of Minnesota.

Definitions

Early onset aGVHD and late aGVHD were defined according to 2005 National Institutes of Health (NIH) consensus criteria [1] and confirmed in the 2014 NIH consensus conference [5]. *Early onset aGVHD* was defined as features of aGVHD, in the absence of cGVHD, with onset before day +100 after HCT. *Late aGVHD* was defined as features of aGVHD observed beyond day +100. This was further classified as *de novo* if new onset of symptoms and signs of aGVHD were seen after day 100, without prior early-onset aGVHD; *recurrent*, if there was recurrence of previously resolved aGVHD after day 100; or *persistent*, if persistent symptoms and signs of aGVHD were seen after day 100 without prior resolution. Acute GVHD was graded according to the established criteria [6]. Grading of late aGVHD followed standard grading of aGVHD [6]. Classic cGVHD was defined according to 2005 NIH consensus criteria [1]. Overlap syndrome was included in the 2005 NIH consensus criteria [1] as a subcategory of cGVHD with overlapping features of both acute and cGVHD, but this nomenclature was not retained in the 2014 NIH consensus conference [5]. As both classic cGVHD and overlap syndrome manifest features of cGVHD, we combined both these categories into cGVHD for the purpose of this analysis.

The regimens for myeloablative (MA) conditioning consisted of cyclophosphamide and fractionated total body irradiation or busulfan and cyclophosphamide, with or without antithymocyte globulin (ATG), or fludarabine-based regimen, with or without ATG [7-10]. MA umbilical cord blood (UCB) recipients also received fludarabine, with or without ATG [10]. Reduced-intensity conditioning (RIC) consisted of cyclophosphamide, fludarabine, and low-dose total body irradiation, with or without ATG [7].

GVHD prophylaxis consisted of cyclosporine (CSA) and mycophenolate mofetil for all RIC and UCB HCT. Methotrexate and either CSA or tacrolimus were used for GVHD prophylaxis in MA HLA-identical sibling donor and adult unrelated donor (URD) HCT recipients. Patients diagnosed with aGVHD were treated with oral prednisone (2 mg/kg daily, or 60 mg/m^2/day or methylprednisolone i.v. equivalent) as initial therapy for 2 weeks and tapered over the next 8 weeks. Patients diagnosed with cGVHD (and reclassified as late aGVHD) were treated as those with cGVHD. Response to treatment was assessed as previously described [11]. *Complete response* (CR) was defined as complete resolution of aGVHD manifestations in all organs, without need for secondary GVHD therapy. *Partial response* (PR) was defined as improvement in GVHD stage in all initially affected organs, without resolution in all organs, worsening in any other GVHD target organs, or need for secondary GVHD therapy. *No response* was defined as the same severity of GVHD in any organ, or death, or the addition of secondary GVHD therapy before day 28. Patients who experienced a flare of aGVHD before day 28 and required therapy with increased steroids or additional GVHD therapy were also considered to have no response. *Progression* was defined as worsening GVHD in at least 1 organ with or without improvement in any other organ [11].

Statistical Analysis

Demographic and clinical characteristics were described using descriptive statistics. Cumulative incidences of late aGVHD, early-onset aGVHD, and cGVHD were estimated with non-GVHD deaths modeled as competing risks [12]. Overall survival (OS) was calculated using Kaplan-Meier estimates and 95% confidence intervals (CIs) were calculated using the Greenwood formula [13]. Cumulative incidence of NRM was calculated using relapse or disease progression of the underlying malignancy as competing risk [12]. Incidences of early onset and late aGVHD were calculated from time of HCT, and outcomes (OS, NRM, and cGVHD) after aGVHD were calculated from onset of early aGVHD for early outcomes or late aGVHD for late outcomes, using day +100 after HCT as the landmark for persistent late aGVHD.

Multiple regression was used to identify factors independently associated with risk of developing late aGVHD (among patients who developed early aGVHD) and risk of OS and NRM (among patients who developed late aGVHD). Cox regression was used for OS and Fine and Gray regression was used for other outcomes using the competing risks defined above [14,15]. Factors tested in regression models included age, underlying disease, disease risk before HCT, conditioning regimen (MA versus RIC), donor/recipient cytomegalovirus serostatus, donor-recipient gender match (female to male versus other), use of ATG in conditioning, stem cell source (marrow versus peripheral blood stem cells versus UCB) and maximum grade of prior early-onset aGVHD (for late aGVHD). All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC) and R 3.0.2.

RESULTS

Baseline Characteristics

Seventy-five (n = 75) patients with late aGVHD and 248 patients with early-onset aGVHD were included in this study. Because 68 patients with early-onset aGVHD developed recurrent or persistent late aGVHD, these groups are not mutually exclusive. Table 1 describes the demographics and transplantation characteristics of patients. No major differences were seen in baseline and HCT characteristics of the 2 groups. The median age at HCT was 50.7 years (range, 19 to 72) in the late aGVHD group and 50.4 years (range, 18 to 75) in the early-onset aGVHD group. The donor source included a fully HLA-matched sibling donor in 41.3% versus 32%, an URD in 13.3% versus 12%, and UCB in 45.3% versus 56%, in late aGVHD and early-onset aGVHD groups, respectively. Non-UCB graft sources included peripheral blood stem cell in 47% and 35% and bone marrow in 8% and 9%, in late aGVHD and early-onset aGVHD groups, respectively. A majority of patients in both cohorts received RIC. The median follow-up of survivors was 4.2 years.

Acute GVHD Characteristics: Late versus Early-onset aGVHD

The cumulative incidence of late aGVHD at 1 year was 14.7% (95% CI, 11.6% to 17.8%), and for early-onset aGVHD, it

Table 1
Baseline Demographics and Transplantation Characteristics

Characteristic	Late aGVHD (n = 75)	Early Onset aGVHD (n = 248)
Age, median (range), yr	50.7 (19-72)	50.4 (18-75)
Gender		
Male	47 (63%)	145 (58%)
Female	28 (37%)	103 (42%)
Diagnosis		
Acute leukemia	35 (47%)	134 (54%)
Chronic leukemia	8 (11%)	25 (10%)
Lymphoma	10 (13%)	31 (12%)
MDS/MPN	16 (21%)	41 (17%)
Multiple myeloma	3 (4%)	12 (5%)
Other	3 (4%)	5 (2%)
Donor type		
HLA-matched sibling	31 (41.3%)	80 (32%)
URD	10 (13.3%)	31 (12%)
UCB	34 (45.3%)	139 (56%)
Graft type		
Marrow	6 (8%)	22 (9%)
PBSC	35 (47%)	87 (35%)
UCB	34 (45%)	139 (56%)
Gender match		
Female donor to male recipient	12 (16%)	53 (21%)
Other	63 (84%)	195 (79%)
CMV serostatus		
Recipient positive	46 (61%)	155 (63%)
Recipient negative	29 (39%)	92 (37%)
Conditioning		
MA	27 (36%)	94 (38%)
RIC	48 (64%)	154 (62%)
GVHD prophylaxis		
CSA/MMF	64 (85%)	200 (81%)
CSA or tacrolimus + MTX	10 (13%)	35 (14%)
Ex vivo T cell depletion	0 (0%)	3 (1%)
Other	1 (1%)	10 (4%)
ATG		
No	55 (73%)	192 (77%)
Yes	20 (27%)	56 (23%)

MDS/MPN indicates myelodysplastic syndrome/myeloproliferative neoplasm; PBSC, peripheral blood stem cells; CMV, cytomegalovirus; MMF, mycophenolate mofetil; MTX, methotrexate.
Data presented are n (%), unless otherwise indicated.