Hematopoietic Stem Cell Transplantation in Patients with Lymphomatoid Granulomatosis: A European Group for Blood and Marrow Transplantation Report

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Lymphomatoid granulomatosis (LG) is a very rare, Epstein-Barr virus–associated lymphoproliferative disorder of B cells. Prognosis is poor, particularly after relapse and no curative treatment exists. We report the results of high-dose therapy and autologous stem cell transplantation (ASCT) or reduced-intensity conditioning and allogeneic stem cell transplantation (alloSCT) in patients with multiply relapsed LG. A European Group for Blood and Marrow Transplantation survey identified 10 patients who had received 9 ASCT and 4 alloSCT. All patients had active disease at the time of transplantation. With a median follow-up of 5.1 (range, 1.4 to 6.3) years, 6 patients are alive and disease-free. Two ASCT patients died of septicemia early after transplantation, and 1 committed suicide after being in continuous complete remission 19 months after ASCT. Another patient allografted 4 years after ASCT remained disease-free but died of severe graft-versus-host disease 3 months after alloSCT. High-dose therapy followed by ASCT and alloSCT are effective therapeutic options and should be considered in all patients with refractory and multiply relapsed LG.

INTRODUCTION

Lymphomatoid granulomatosis (LG) is a very rare, Epstein-Barr virus (EBV)-driven B cell lymphoproliferative disorder first described as a distinct clinicopathological entity by Liebow in 1972 [1]. At diagnosis, the majority of patients are between 40 and 60 years of age with a definite male preponderance. Immunocompromised patients are more likely to develop LG, probably because cellular immunodeficiency compromises EBV elimination. Three histological grades have been described, depending on the number of EBV-positive, CD-20 positive, large atypical B cells in relation to reactive tissue. Whereas grade 1 lesions contain very few and grade 2 lesions contain only scattered EBV-positive cells, grade 3 lesions are characterized by sheets of large atypical cells showing a high propensity to transform into diffuse large B cell lymphoma [2]. Because of lung involvement in >90% of cases, first symptoms are often cough and shortness of breath in combination with B symptoms, such as fever, night sweats, and weight loss. The skin, kidneys, liver, and the central nervous system are affected in about one third of the patients, although involvement of lymph nodes or spleen is rare. In older series, median survival of patients with LG was under 2 years [3,4]. Patients with grade 1 or 2 lesions may achieve durable remissions with corticosteroids and interferon-alpha [5]. Dunleavy et al. investigated the use of interferon-alpha in 28 patients with grade 1/2 disease and achieved a 5-year progression-free survival of 56%. In 24 patients with grade 3 disease, progression-free survival was 40% with dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone ± Rituximab (DA-EPOCH±R) with a median follow up of 28 months [6]. Despite a number of case reports, there are no reliable data available if aggressive first-line therapy, including combination chemotherapy with or without rituximab, can improve outcome of patients with advanced disease as recently reviewed [6-8]. Patients with relapsed disease often demonstrate higher histologic grades and carry a very bad prognosis with no curative approach having been described. Because case reports of high-dose therapy followed by autologous stem cell transplantation (HDT/ASCT) [9,10] or allogeneic stem cell transplantation (alloSCT) [11] indicated

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Table 1
Patients Characteristics

Patient	Age*/ Gender	Stage†/Grade	Sites of Disease†/Yr of Diagnosis	Lines of Therapy	Preparatory Regimen	Transplant/Time from Diagnosis to Transplantation (mo.)	Disease Status†	Best Response after Transplantation	Relapse	Outcome
1	38/F	IV A/3	Lung/2005	R-CHOP R-I, MTX, E	BEAM	Auto/7	PR	PR	Yes	Received second auto
					Z-BEAM	Auto	Relapse	CR	No	A&W, d +1456
2	48/M	I_E B/1	Lung/2007	Pred R R-CHOP	BEAM	Auto/16	SD	Autopsy: no evidence of LG	No	Died, d +8: septicemia, VOD
3	37/F	IV/not known	Lung, liver, lymph nodes/2004	CHOP DHAP ICE	BEAM	Auto/7	PR	CR	Yes	NA
					FM	Allo	NE	NA	No	Died, d +1567: GvHD
4	53/F	IV B/2	Lung, liver, lymph nodes/2007	Cy-Dex R-CHOP DHAP α-IFN HD-Cy	FBC[12]	Auto/9	SD	CR	No	A&W, d +1864
5	31/F	II A/not known	Lymph nodes/2002	V-CAMP R-ICE	FBC	Allo/52	PR	CR	No	A&W, d +1554
6	19/M	IV A/3	Bone marrow, lymph nodes/2001	COPADM-COPAD R DHAP-VIM-DHAP	BEAM	Auto/52				
					FM[18]	Allo	PR	CR	No	A&W, d +2119
7	34/M	IV B/2	Lung, CNS/2004	R HD-MTX AraC[16]	FM[18]	Allo/13	PD	not known	No	A&W, d +2314
8	31/M	IV A/2/3	Lung/2000	Pred Cy CHOP	BEAM[5]	Auto/10	PR	CR	No	Died, d +576: suicide
9	53/M	IV B/2/3	Lung/2005	R-CHOP ASHAP	TMC	Auto/5	PD	PD	not known	Died, d +9: PD, sepsis
10	49/F	IV B/1	Lung, liver, CNS, adrenals, kidney/2011	R-CHOP MTX R-IE, AraC	TC/TBI	Auto/5	PR	PR	No	A&W, d +502

R indicates rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; I, ifosfamide; MTX, methotrexate; E, etoposide; BEAM, BCNU, etoposide, cytosine-arabinoside, melphalan; Z-BEAM, Zevalin+BEAM; Pred, prednisone; DHAP, dexamethasone, cytosine-arabinoside, adriamycin, methotrexate, prednisone; ICE, ifosfamide, cyclophosphamide, etoposide; Cy, cyclophosphamide; IFN, interferon; FBC, fludarabine, busulphan, cyclophosphamide; V-CAMP, vincristine, cyclophosphamide, adriamycin, methotrexate, prednisone; COPADM-COPAD, cyclophosphamide, vincristine, prednisone, doxorubicin, dexamethasone, methotrexate; VIM, VP-16, ifosfamide, methotrexate; AraC, cytosine-arabinoside; ASHAP, adriamycin, solumedrol, cytosine-arabinoside, platinum; FM, fludarabine, melphalan; TMC, thiotepa, melphalan, carboplatinum; TC/TBI, thiotepa, cyclophosphamide, total body irradiation; A&W, alive and well; PR, partial remission; PD, progressive disease; d, day; GvHD, graft-versus-host disease; VOD, veno-occlusive disease.

* At time of transplantation.

† At diagnosis.

that patients with LG might benefit from these procedures, we aimed to collect all cases of autologous and allogeneic transplantation reported to the EBMT to gain better insight into the therapeutic impact of transplantation in this rare disease.

PATIENTS AND METHODS

The European Group for Blood and Marrow Transplantation (EBMT) is a voluntary organization currently comprising 545 transplantation centers. All member centers are required to report all new hematopoietic stem cell transplantations and follow-up data once per year. The Lymphoma Working Party is responsible for data validation to ensure the quality of data. Because LG is not listed as a distinct histological entity on case report forms, we invited all EBMT centers to contribute data on their patients with a confirmed diagnosis of LG as defined by the WHO classification [2].

We identified 10 patients who had undergone 13 (9 autologous and 4 allogeneic) transplantations. All centers completed an extensive questionnaire for each eligible patient. Data for individual patients were derived both from the EBMT database and the questionnaires sent out to the centers. Follow-up questionnaires were sent to obtain missing data. Informed consent was obtained locally according to regulations applicable at the time of transplantation. After January 2003, EBMT centers were required to obtain written informed consent before data registration. In addition to the European cases, we updated a case from Canada, which had previously been published [9].

RESULTS AND DISCUSSION

The major patient characteristics, lines of treatment, and outcomes are summarized in Table 1. The patient cohort finally consisted of 5 females and 5 males, ages between 19 and 53 years at the time of transplantation. Eight of 10 patients had been diagnosed with stage IV disease; the lungs were the most frequently involved extranodal site (8 of 10 patients) but involvement of liver, CNS, kidneys, adrenals, and bone marrow was also described. All patients had received at least 2 lines of therapy before transplantation, including rituximab in 7 patients. The median time interval from diagnosis to stem cell transplantation was 9.5 (range, 5 to 52) months. All patients had active disease at the time of stem cell transplantation: 6 patients were in partial remission immediately before their first transplant, 2 had stable disease, and 2 presented with progressive disease. Eight patients received HDT/ASCT as their first transplantation; 1 of these patients (patient 1) received a second autologous transplant after HDT including ibritumomab tiuxetan (Zevalin), another patient (patient 6) had a planned double transplant procedure: BEAM/ASCT was followed by reduced-intensity conditioning (RIC) and alloSCT from a matched unrelated donor. Three more patients (patients 3, 5, 7) received allografts after RIC, 1 of them because of relapse after HDT/ASCT (patient 3). The stem cell donor was an HLA-matched sibling in 1 and a matched unrelated donor in the remaining 2. Five of the 8 ASCT patients received their transplantation after BEAM, the other patients received other HDT including thiotepa, melphalan, and carboplatinum; fludarabine, busulfan and cyclophosphamide; or total body irradiation in combination with thiotepa and cyclophoshamide. All conditioning regimens before allogeneic transplantation were of reduced intensity (see Table 1).

With a median follow up of 5.1 (range, 1.4 to 6.3) years for surviving patients, 6 of 10 patients are alive with no evidence of disease. Notably, only 2 patients relapsed after transplantation; 1 of these patients is in continuous complete remission for almost 4 years after a second ASCT, the other patient died 3 months after allogeneic transplantation from severe graft-versus-host disease of the gut; at this time, histology was diffuse large B cell lymphoma rather than LG.

Two ASCT patients died of septicemia on days +8 or +9 after transplantation; no evidence of LG was found at the autopsy in 1 of these patients, the other patient had evidence of progressive disease after ASCT. Unfortunately, patient 8 committed suicide 19 months after ASCT while being in remission from LG.

In summary, 6 patients remain alive and well 5.1 (1.4 to 6.3) years after HDT/ASCT or RIC/alloSCT (3 patients each). One patient committed suicide with no evidence of LG at that time and 2 patients died of transplantation-related complications (septicemia) early after HDT/ASCT. One of these patients was reported as being refractory to salvage therapy before HDT/ASCT. A correlation between time from diagnosis or status of disease before transplantation and outcome does not exist, possibly due to small numbers. Given the number and the nature of prior therapies (including rituximab in 7 patients) and the status of disease before transplantation, we consider the results achieved with HDT/ASCT and/or RIC/alloSCT promising in a disease believed to carry a poor prognosis at diagnosis but certainly so in multiply relapsed or refractory patients.

This study represents the first, albeit small, series of patients who underwent transplantation for LG, a disease so exceedingly rare that until now, only case reports for first-line and certainly for treatment of relapsed cases have been published.

With only 10 patients reported here, our series may be biased by over-reporting of successful cases, although we explicitly asked EBMT members to report all cases from their institutions. It also is not possible to decide if autologous or allogeneic transplants should be preferred or to comment on details of the transplant procedure, such as the best choice of the preparatory regimen, donor selection, or graft-versus-host disease prophylaxis for allografted patients. Nonetheless, HDT/ASCT and RIC/alloSCT showed promising results in this small series of advanced LG patients and should be considered for relapsed and otherwise refractory patients fit enough to undergo any of these procedures.

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Reciprocal Expression of Enteric Antimicrobial Proteins in Intestinal Graft-Versus-Host Disease

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We recently demonstrated that expression of α-defensins, the major antimicrobial peptides produced by Paneth cells, was severely suppressed in mice with graft-versus-host disease (GVHD). In this study, we found that antibacterial lectin, regenerating islet-derived IIIγ (RegIIIγ) was upregulated in villous enterocytes, thus demonstrating the reciprocal control of enteric antimicrobial proteins in GVHD. Upregulation of RegIIIγ was mediated by a mechanism independent upon radiation-induced intestinal tract damage. MyD88-mediated signaling in intestinal epithelium was required for RegIIIγ upregulation in GVHD and antibiotic therapy downregulated RegIIIγ expression. These results suggest that MyD88-mediated sensing of the intestinal microbes disregulated in GVHD induces RegIIIγ upregulation in GVHD and argue a role for RegIIIγ in the pathogenesis of GVHD.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation, a curative therapy for a number of hematologic diseases, is complicated by graft-versus-host disease (GVHD). Particularly, intestinal GVHD is critical for determining the outcome of allogeneic bone marrow transplantation (BMT) [1]. Recently, regenerating islet-derived 3α (RegIIIα) was identified as a specific biomarker for intestinal GVHD in humans using a large-scale and quantitative proteomic discovery approach [2,3]. Reg genes constitute a multigene family, which is categorized into 4 subclasses. RegIIIγ, a homologue of human RegIIIα in mice, is preferentially expressed in the small intestine. RegIIIγ have canonical C-type lectin domains that bind to the peptidoglycan, which is an essential component of the bacterial cell wall and, thus, has direct antimicrobial activity, specifically against Gram-positive bacteria and protects the epithelial barrier function of the intestinal mucosa [4].

The intestinal microbial communities are actively regulated by Paneth cells through their secretion of antimicrobial peptides. Among them, α-defensins are the most potent antimicrobial peptides that account for 70% of the bactericidal peptide activity released from Paneth cells [5,6]. We recently found that Paneth cells were targeted by GVHD, resulting in marked reduction in the expression of α-defensins [7]. Thus, it is puzzling why blood levels of RegIIIα levels are elevated, whereas α-defensins are downregulated, in GVHD. In this study, we evaluated enteric expression of RegIIIγ at the cellular level in mouse models of BMT and found that the major producers of RegIIIγ were villous enterocytes, not Paneth cells, in GVHD. Upregulation of RegIIIγ in GVHD was dependent upon MyD88-mediated sensing of the intestinal microflora.

MATERIAL AND METHODS

Mice

Female C57BL/6 (B6: H-2^b), B6D2F1 (H-$2^{b/d}$), B6-Ly5.1 (H-2^b, CD45.1^+), BALB.B (H-2^b), and C3H.Sw (H-2^b) mice were purchased from Charles River Japan, KBT Oriental, or Japan SLC. B6-background Myeloid differentiation factor 88 (MyD88)-deficient (MyD$88^{-/-}$) mice [8] were kindly provided by Dr. Kiyoshi Takeda at Osaka University. All animal experiments were performed under the auspices of the Institutional Animal Care and Research Advisory Committee.

BMT

Mice underwent transplantation as previously described [9]. In brief, after lethal X-ray total body irradiation delivered in 2 doses at 4 hour intervals, mice were intravenously injected with 5×10^6 T cell–depleted bone marrow (TCD-BM) cells with or without 2×10^6 splenic T cells on day 0. Isolation of T cells and T cell depletion were performed using the T cell isolation kit and anti-CD90-MicroBeads, respectively, and the AutoMACS (Miltenyi Biotec, Tokyo, Japan) according to the manufacturer's instructions.

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