Biol Blood Marrow Transplant 20 (2014) 1751–1757

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Incidence, Risk Factors, and Long-Term Outcomes of Sclerotic Graft-versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation

Jieun Uhm [1], Nada Hamad [1], Elizabeth M. Shin [2], Fotios V. Michelis [1], Mohamed Shanavas [1], Vikas Gupta [1], John Kuruvilla [1], Jeffrey H. Lipton [1], Hans A. Messner [1], Matthew Seftel [1], Dennis (Dong Hwan) Kim [1,*]

[1] *Allogeneic Blood and Marrow Transplant Program, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Department of Medicine, University of Toronto, Toronto, Ontario, Canada*
[2] *School of Medicine, University of Toronto, Toronto, Ontario, Canada*

Article history:
Received 9 June 2014
Accepted 1 July 2014

Key Words:
Chronic graft-versus-host disease
Sclerosis
Allogeneic hematopoietic stem cell transplantation

A B S T R A C T

Sclerotic chronic graft-versus-host disease (sclGVHD) is associated with significant morbidity and a poor quality of life. We reviewed 502 patients diagnosed with chronic GVHD and analyzed the incidence and risk factors of sclGVHD and long-term outcomes and immunosuppressive therapy (IST) cessation in patients with sclGVHD. With a median onset at 18 months the cumulative incidence of sclGVHD was estimated at 22.6% at 5 years (95% confidence interval, 18.6% to 26.8%). Univariate and multivariate analysis identified 2 risk factors for sclGVHD: non-T cell depletion (hazard ratio [HR] 9.09, $P < .001$) and peripheral blood stem cell (HR 3.87, $P < .001$). Overall survival (OS) at 5 years was significantly better in the sclGVHD group (88.1%) compared with the non-sclGVHD group (62.7%; $P < .001$), as were nonrelapse mortality (7.3% versus 21.5% at 5 years) and relapse rates (9.1% versus 19.3% at 5 years). There was no difference in the rate of IST cessation at 5 years (44.8% versus 49.9%, $P = .312$), but there was a trend of longer IST duration in the sclGVHD group compared with the non-sclGVHD group (median 71.6 months versus 62.9 months). In conclusion, T cell depletion and graft source affect the risk of sclGVHD. SclGVHD did not adversely affect long-term outcomes or IST duration.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a significant cause of morbidity and mortality of allogeneic hematopoietic cell transplantation (allo-HCT), resulting in a higher risk of late nonrelapse mortality (NRM) and poor quality of life [1,2]. The National Institutes of Health (NIH) proposed consensus criteria for the diagnosis and staging of cGVHD based on clinical manifestations, which are now widely used in clinical practice [3]. These criteria identify sclerotic cGVHD (sclGVHD) as a distinctive phenotype of cGVHD with sclerotic features in the skin characterized by thickened, tight, and fragile skin [3]. SclGVHD includes several cutaneous presentations resembling morphea, systemic sclerosis, or eosinophilic fasciitis [4].

SclGVHD may cause significant morbidity and disability because it is often associated with poor wound healing, inadequate lymphatic drainage, skin ulcers from minor trauma, and joint contractures, but there are only a few studies that described its clinicopathological features and risk factors [4-8]. The incidence of sclGVHD has been reported to be 15% to 20% among patients with cGVHD [5,7,8], and a large cross-sectional study of single-patient visits for the evaluation of severe cGVHD reported it to be as high as 53% [4]. Because sclGVHD usually occurs late in the course of cGVHD, it may result in the need for prolonged systemic immunosuppressive therapy (IST) with multiple agents [4,5,7] and consequently adversely affect long-term outcomes [4,8]. However, because long-term outcomes of sclGVHD have not been investigated recently, the question of whether sclGVHD patients have an adverse prognosis with higher mortality has not been answered. Therefore, we conducted an institutional retrospective study of patients who developed cGVHD to analyze the incidence, clinical risk factors of sclGVHD, long-term outcomes, IST treatment failure, and IST cessation rates in patients who developed sclGVHD.

Financial disclosure: See Acknowledgments on page 1757.
* Correspondence and reprint request: Dennis (Dong Hwan) Kim, MD, PhD, Allogeneic Blood and Marrow Transplant Program, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, 610 University Ave. Toronto, Ontario M5G2M9, Canada.
E-mail address: dr.dennis.kim@uhn.ca (D.(D.H.) Kim).

http://dx.doi.org/10.1016/j.bbmt.2014.07.001
1083-8791/

METHODS

We reviewed 502 consecutive patients diagnosed with cGVHD between January 2000 and October 2012 at the Princess Margaret Cancer Centre, Toronto, Canada. We reclassified cGVHD according to the NIH consensus criteria [3], particularly with respect to the date of onset of cGVHD, involved organs, the severity of cGVHD, ISTs for the treatment of cGVHD, and the cessation of ISTs. The research ethics board at the University Health Network approved this study.

In the 502 patients, median time of onset was 4.8 months after allo-HCT (range, 2.1 to 48.8). Ninety-six patients (19.1%) were diagnosed with sclGVHD. There were 358 survivors with a median follow-up time of 60.7 months (range, 2.7 to 159.1). Patient and transplant-related characteristics are summarized in Table 1.

Definition of sclGVHD

SclGVHD was defined as sclerodermatous skin lesions with either deep or superficial sclerotic features on physical examination, fasciitis demonstrated on magnetic resonance image, or joint contracture on physical examination documented in medical records as previously described [3,5]. The overall severity of cGVHD and the severity of organ-specific cGVHD (skin, mouth, eyes, gastrointestinal tract, liver, lungs, joints and fascia, and the female genital tract) were graded using the NIH consensus criteria [3].

Transplant Procedures

For related donors, HLA-A, -B, and -DR were screened, and for unrelated donors HLA-C and -DQ were added. Unrelated donors of peripheral blood stem cells (PBSCs) or bone marrow cells were identified through the One-Match Stem Cell and Marrow Donor Network.

Patients received conditioning regimens before HCT infusion as per institutional protocols [9,10]. Related donor transplants were not T cell depleted (TCD), but unrelated donor transplants were TCD in vivo using alemtuzumab. GVHD prophylaxis consisted of cyclosporine (administered for 3 months in related donor transplants unless GVHD required further treatment and for 6 months in unrelated donor transplants), combined with either methotrexate (15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11 after allo-HCT) or mycophenolate mofetil (15 mg/kg every 8 hours until day +30) [9].

The first line treatment for acute GVHD (aGVHD) included oral prednisone or intravenous methylprednisolone (equivalent to 2 mg/kg/day of methylprednisolone). The treatment of cGVHD was decided after considering the individual patient's clinical status and IST. Steroid therapy was used as first-line treatment for those already on IST, whereas either steroids, cyclosporine, or both agents in combination were used for patients receiving IST. When additional treatment was indicated because of resistance to previous lines of IST, a flare of GVHD, or intolerance, second or further lines of IST were introduced according to each patient's clinical manifestations or toxicity profiles. Theses salvage regimens included azathioprine, mycophenolate mofetil, tacrolimus, extracorporeal photopheresis, rituximab, or combination therapy [11].

Statistics

Overall survival (OS) and GVHD-specific survival (GSS) were calculated using the Kaplan-Meier method with a log rank test. OS was defined as date

Table 1
Patient, Disease, and Transplant Characteristics

	cGVHD (n = 502)	sclGVHD (n = 96)	Nonsclerotic (n = 406)	*P*
Median age at the transplant, yr (range)	48 (18-70)	45 (19-68)	49 (18-70)	
Gender, no. (%)				
Male	291 (58)	51 (53)	240 (59)	.302
Female	211 (42)	45 (47)	166 (41)	
Gender mismatch, no. (%)				
Male to male	134 (27)	23 (24)	111 (27)	.357
Male to female	89 (18)	16 (17)	73 (18)	
Female to male	115 (23)	21 (22)	94 (23)	
Female to female	93 (19)	25 (26)	68 (17)	
Missing	71 (14)	11 (12)	60 (15)	
Disease, no. (%)				
AML	199 (40)	27 (28)	172 (42)	.006
ALL	50 (10)	14 (15)	36 (9)	
Acute leukemia	5 (1)	0 (0)	5 (4)	
MDS	48 (10)	12 (13)	36 (9)	
CML	55 (11)	14 (15)	41 (10)	
MF/MPD	34 (7)	4 (4)	30 (7)	
CLL	31 (6)	13 (14)	18 (4)	
Malignant lymphoma	63 (13)	10 (10)	53 (13)	
AA	14 (3)	2 (2)	12 (3)	
Others	3 (1)	0 (0)	3 (1)	
Intensity of conditioning regimen, no. (%)				
Myeloablative	358 (71)	74 (77)	284 (70)	.209
Nonmyeloablative	144 (29)	22 (23)	122 (30)	
HLA and donor type, no. (%)				
Related	345 (69)	78 (81)	267 (66)	.001
Matched unrelated	134 (27)	18 (19)	116 (29)	
Mismatched unrelated	23 (5)	0 (0)	23 (6)	
Stem cell source, no. (%)				
Bone marrow	102 (20)	10 (10)	92 (23)	.007
Peripheral blood	400 (80)	86 (90)	314 (77)	
TCD, no. (%)				
Depleted	86 (17)	3 (3)	83 (20)	<.001
Not depleted	416 (83)	93 (97)	323 (80)	
TBI in conditioning, no. (%)				
None	106 (21)	19 (20)	87 (21)	.010
≤400 cGy	215 (43)	30 (31)	185 (46)	
>400 cGy	181 (36)	47 (49)	134 (33)	
GVHD prophylaxis, no. (%)				
CyA/MTX ± TCD	235 (47)	61 (64)	174 (43)	<.001
CyA/MMF ± TCD	195 (39)	31 (32)	164 (40)	
CyA/TCD	63 (13)	2 (2)	61 (15)	
Others	9 (2)	2 (2)	7 (2)	

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; MF, myelofibrosis; MPD, myeloproliferative disorder; CLL, chronic lymphocytic leukemia; AA, aplastic anemia; TBI, total body irradiation; CyA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil or mycophenolate sodium.