Sclerodermatous chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation: incidence, predictors and outcome

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Scleroderma may be one of the most severe forms of chronic graft-versus-host disease (GVHD). We retrospectively evaluated its incidence, predictor variables and outcome in 133 patients who survived at least 4 months after allogeneic hematopoietic stem cell transplantation. The 5-year cumulative incidence was 15.5% in patients with chronic GVHD. The generalized form had a progressive course despite immunosuppressive therapy. Eosinophilia, autoimmune markers, and previous skin involvement by chronic GVHD with disorders of pigmentation were significantly associated with an increased probability of developing scleroderma.

Key words: scleroderma, chronic graft-versus-host disease, allogeneic hematopoietic stem cell transplantation.

Haematologica 2006; 91:258-261

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Chronic graft-versus-host disease (GVHD) is the most common late complication of allogeneic hematopoietic stem cell transplantation (HSCT).[1] The sclerodermatous form shows many analogies with systemic sclerosis and is characterized by skin fibrosis.[2-4] Its severe forms affect patient's mobility and overall quality of life.[2-4] Scleroderma is often refractory to standard and secondary therapy.[1-3] In this paper, we describe the incidence and outcome of sclerodermatous chronic GVHD in 174 patients. We also tried to identify predictors of this particular form of chronic GVHD.

Design and Methods

We retrospectively analyzed 174 patients who underwent allogeneic HSCT between January 1992 and December 2003. The incidence of sclerodermatous chronic GVHD was evaluated in 133 patients who survived at least 4 months after transplantation. The patients' characteristics are shown in Table 1. The diagnosis and grading of acute and chronicGVHD were primarily based on clinical findings and followed the commonly accepted diagnostic criteria.[5,6] Extensive chronic GVHD was treated with 3-5 mg/kg/day cyclosporine A and 1-2 mg/kg/day prednisone in patients already receiving cyclosporine A therapy. Cyclosporine A was used alone in patients off immunosuppression at time of the onset of extensive chronic GVHD. Patients with mild/moderate extensive chronic GVHD and with a high risk of relapse were not treated. Except for the sclerodermatous form, refractory extensive chronic GVHD was treated in three patients with cyclosporine A plus prednisone and tacrolimus or mycophenolate mofetil. Patients were clinically examined weekly during the first 3 months, every 2 weeks until 1 year after HSCT and monthly afterwards. We also screened the patients for autoimmune markers such as antinuclear antibodies, anti-double-stranded DNA, anti-extractable nuclear antigens, anti-mitochondria, anti-smooth muscle, anti-cardiolipin, lupus anticoagulants, anti-thyroglobulin, antimicrosomal, every 6 months during the first year, then every 6-12 months. The assessment of skin involvement by chronic GVHD was made on the basis of the previously described criteria[2-4,6] and supported by the examination of an expert dermatologist. The skin lesions in chronic GVHD were classified as: (i) lichenoid lesions; (ii) sclerodermatous lesions, including cutaneous changes mimicking eosinophilic fasciitis[4,7]; (iii) disorders of pigmentation such as areas of hypopigmentation and hyperpigmentation, which could be isolated or associated with lichenoid and/or sclerodermatous lesions,[1,4] and leopard skin eruption (widespread, well-delimited, hyperpigmentated macules).[3] Histological examination was necessary to make the diagnosis of scleroderma in two cases. Sclerodermatous chronic GVHD was defined as generalized if more than two anatomic sites were involved and as localized in the remaining cases. To assess the extent of skin involvement, the modified Rodnan skin score was used, whereby 17 body areas are palpated and scored on the following scale: 0=normal, 1=thickened, 2=thickened, unable to move, and 3=thickened, unable to pinch (maximum score=51).[8] Response to therapy was defined complete if less than 2% of the skin surface showed tightness, with disappearance of all other active signs attributable to chronic GVHD. Patients who did not show any improvement or those who showed a progression of the sclerotic changes were defined as non-responsive. The response was defined as partial in the remaining cases. The occurrence of sclerodermatous chronic GVHD was estimated by cumulative incidence rates.[9] Overall survivalwas calculated by the Kaplan-Meier method; comparisons between probabilities in different groups of patients were performed using the log-rank test.[10] A Cox proportional hazard regression model was used for univariate and multivariate analysis of predictive vari-

Table 1. Clinical characteristics of 133 patients surviving at least 4 months after HSCT.

Clinical characteristics	*N. of patients*	*%*
Age at HSCT (years)	36	
median (range)	(14-65)	
Sex		
Male	81	61
Female	52	39
Diagnosis		
Acute myeloid leukemia	46	35
Acute lymphoblastic leukemia	27	20
Chronic myeloid leukemia	32	24
Lymphoma	12	9
Chronic lymphoid leukemia	2	2
Multiple myeloma	7	5
Other	7	5
Disease status		
Early phase	71	53
Late phase	62	47
Donor		
Matched related donor	86	65
Matched unrelated donor	47	35
HLA match	124	93
Sex match	66	50
Conditioning regimen		
BU+CY	77	58
TBI+CY	56	42
GVHD prophylaxis		
CyA+MTX	133	100
Source of stem cells		
Bone marrow	89	67
Peripheral blood	44	33
Acute GVHD		
Grade ≥ II	40	30
Grade III-IV	11	8
CMV antigen positive	46	35

Other: idiopathic myelofibrosis, myelodysplastic syndrome, marrow aplasia; early phase: acute leukemia in first remission, chronic myeloid leukemia in chronic phase, untreated disease; late phase: acute leukemia in second or further remission, chronic myeloid leukemia in blastic phase, pre-treated chronic lymphocytic leukemia, lymphoma and myeloma; TBI: total body irradiation; CY: cyclophosphamide; BU: busulphan; MTX: methotrexate 15 mg/m² on day 1, 10 mg/m² on day 3,6,11; CMV: cytomegalovirus.

ables of sclerodermatous chronic GVHD.[11] Variables found to be significant ($p<0.05$) in univariate analysis were tested in multivariate analysis. The following variables were analyzed at time of transplant: age at HSCT, sex, phase of the disease at HSCT (early or late), type of donor (related or unrelated), HLA match, sex match, type of conditioning regimen (based or not on total body irradiation), source of stem cells, CD34 and CD3 cell dose infused. Patient and transplant-related variables were then analyzed at the time of chronic GVHD together with the following: skin involvement by acute GVHD, chronic extensive GVHD (extensive independently of scleroderma), skin and skin-type involvement by chronic GVHD (lichenoid or disorders of pigmentation), mucosae (mouth, gut, eyes or vagina), liver or lung involvement by chronic GVHD, cytomegalovirus antigenemia, donor lymphocyte infusions, presence of autoimmune markers, eosinophils count >500/μL, and lactate levels >500 U/L. An increase of eosinophil count (>500/μL) or lactate dehydrogenase levels (>500 U/L) was considered only if it lasted at least 1 month and occurred 1 to 6 months before the onset of scleroderma and after HSCT. Continuous variables were categorized as follows: each variable was first divided into four categories by approximately the 25th 50th and 75th percentiles. If the hazard ratios (HR) in two or more adjacent categories were not substantially different, these categories were grouped together. If no clear pattern was observed, the median was taken as the cut point. The χ^2 test was used to compare differences in percentages, and the Mann-Whitney U test was used to compare continuous values. All p values were two-sided and $p<0.05$ was considered statistically significant.

Table 2. Clinical characteristics of sclerodermatous chronic GVHD and treatment outcome.

N. of patient	*Sex*	*Age at HSCT*	*Donor*	*Conditioning regimen*	*Source of SC*	*cGVHD grade*	*HSCT-scleroderma onset interval**	*Skin pattern*	*Skin pigmentation disorders*	*Joint contractures*	*Skin score°*	*Autoimmune markers*	*Eosinophilia§ and/or LDH increase*	*Therapy*	*Response Outcome FU**
1	F	49	MRD	Bu+CY	PB	e	15, off IS	G	hyperpigmentation	wrists	20	anti-nuclear	both	CyA+PDN CyA+MTX	NR, 27 alive
2	F	59	MRD	Bu+CY	PB	e	5, off IS G		hyperpigmentation	no	14	no	no	CyA+PDN	NR,†44 relapse
3	M	28	MRD	Bu+CY	PB	e	15, off IS	G	hypo- and hyperpigmentation bullous lesions ulceration	all joints	49	anti-nuclear	LDH	CyA+PDN CyA+MTX	NR,†22 scleroderma IP,CMV-pneumonia
4	F	28	MUD	TBI+CY	BM	e	20, off IS	G	hypo-and hyperpigmentation nodular dermal mucinosis hyperpigmentation	all joints	48	ACLA anti-thyrog	eosinophilia	CyA+PDN CyA+MTX+ECP CyA+PDN+MMF CyA+PDN+anti-CD20	NR,†41 scleroderma
5	M	16	MUD	TBY+CY	BM	e	11, off IS	G		shoulders	35	anti-nuclear	both FK+PDN+thalidomide	FK+PDN	NR,† 16 scleroderma IP, TTP
6	M	22	MUD	TBI+CY	BM	e	12, in IS	G	hypo-and hyperpigmentation ulceration	all joints	47	anti-nuclear	both	CyA+PDN CyA+PDN+FK	NR,†15 scleroderma IP respiratory failure
7	M	51	MRD	Bu+CY	PB	e	13, in IS	L	hyperpigmentation ulceration	no	9	anti-nuclear	eosinophilia	CyA+PDN	PR, †21 pulmonary mycosis
8	F	27	MRD	Bu+CY	BM	e	18, off IS	L	hyperpigmentation	no	10	no	no	CyA+MTX	CR, 110 alive
9	M	32	MUD	TBI+CY	PB	e	23, in IS	L	hypo-and hyperpigmentation	no	10	anti-nuclear	LDH	CyA+MTX	CR, 36 alive
10	M	27	MUD	TBI+CY	BM	e	54, off IS	L	hyperpigmentation	no	10	anti-nuclear, LAC	both	CyA+PDN	PR, 70 alive ACLA, dsDNA
11	F	17	MUD	TBI+CY	PB	l	13, in IS	G	no	shoulders elbows	16	anti-nuclear	both	CyA+PDN	PR, 23 alive CyA+MTX
12	M	19	MUD	TBI+CY	PB	e	25, off IS	L	hyperpigmentation	no	10	anti-nuclear	no	CyA, CyA+MTX	PR, 40 alive
13	F	25	MRD	Bu+CY	BM	l	42, off IS	L	hyperpigmentation	no	8	no	both	CyA+MTX	CR, 159 alive
14	F	19	MUD	TBI+CY	PB	l	15, off IS	L	no	no	3	anti-nuclear	eosinophilia	PDN, MTX	CR,40alive

*MRD, matched related donor; MUD, matched unrelated donor; Bu, busulphan; CY, cyclophosphamide; TBI, total body irradiation; PB, peripheral blood; BM, bone marrow; FU: follow-up; l: limited chronicGVHD; e: extensive chronicGVHD independently of scleroderma or before its onset; IS: immunosuppression; G: generalized; L: localized; ACLA: anticardiolipin antibodies; anti-thyrog: anti-thyroglobulin; LAC: lupus anticoagulants; CYA, cyclosporine A; PND, prednisone; MTX, methotrexate; ECP: extracorporeal photochemotherapy; MMF: mycophenolate mofetil; FK: tacrolimus; anti-CD20: anti-CD20 monoclonal antibody; NR: no-response; PR: partial response; CR: complete response; IP: interstitial pneumonia; TTP: thrombotic thrombocytopenic purpura; *: months; °: modified Rodnan skin score; §: eosinophils >500/μL and LDH >500U/L; †: death.*

Results and Discussion

Of the 133 patients analyzed, 100 (75%) developed chronicGVHD and 14 (10.5%) showed sclerodermatous features at a median of 15 months after transplantation (range, 5-54). The 5-year cumulative incidence of sclerodermatous chronic GVHD was 11.5% (95% CI, 7-19%) in all transplanted patients and 15.5 % (95% CI, 10-25) in those with chronic GVHD. The clinical characteristics of patients are summarized in Table 2. Before the onset of scleroderma, the skin was involved by chronic GVHD with lichenoid lesions (21%) and disorders of pigmentation such as hypo-hyperpigmentation (50%) and leopard skin eruption (29%). Ten patients (71%) were off immunosuppressive therapy when scleroderma developed and three had received donor lymphocyte infusions because of relapse. None had Raynaud's phenomenon. Lung involvement (fibrosis and interstitial pneumonia in patients n. 3-6), occurred only in the generalized form. Since the shortest time for the development of sclerodermatous chronic GVHD was 5 months, in the analysis of predictive variables we considered only the 126 patients surviving more than 5 months. Results from the univariate analysis at the the time of HSCT and at the time of chronicGVHD are shown in Table 3. CD3 cell dose was a significant predictor at time of HSCT in multivariate analysis (HR=6.4, 95% CI:1.5-27.2; p=0.01). Previous skin involvement by chronic GVHD, such as disorders of pigmentation (HR=6.5, 95% CI:1.6-26.3; p=0.008), eosinophilia (HR=7.1, 95% CI: 2.2-23; p=0.001) and autoimmune markers (HR=6.3, 95% CI: 1.6-24.2; p=0.008) were significant predictors at the time of chronic GVHD in multivariate analysis. The first line therapy was mostly cyclosporine A plus prednisone (57%) or plus methotrexate (22%) (Table 2). The total weekly dose of methotrexate was between 15 and 30 mg and was given i.v. or i.m. fractionated in two or three doses. Cyclosporine A plus methotrexate was used as salvage therapy in six patients. All patients with generalized scleroderma but one (responsive to second line cyclosporine A plus methotrexate) were unresponsive to standard and salvage therapy. All patients with limited scleroderma were responsive (71% to methotrexate-based therapy). We compared the clinical characteristics between patients with sclerodermatous chronic GVHD who responded (completely or partially) to immunosuppressive therapy and those who were non-responsive. Non-responsive patients more frequently had generalized scleroderma (100% vs 12%, p=0.004) with lung involvement (67% vs 0%, p=0.01), had a higher skin score (median: 41 vs 10; p=0.003) and showed an earlier onset of disease after HSCT (13.5 vs 20.5 months; p=0.05). Among patients with chronic GVHD, the 5-year probability of overall survival for patients with sclerodema (43%) was worse than for those without (60%), but the difference was not statistically significant (p=0.25). Chronic GVHD is the most common non-relapse problem affecting long-term survivors of HSCT.[1] Skin involvement is an unfavorable prognostic factor, together with thrombocytopenia, progressive onset, poor performance status, and gastrointestinal involvement.[6,12] Sclerodermatous chronic GVHD is a type of skin involvement which has been described in small series of patients particularly by dermatologists.[2-4] In our study, the rate of sclerodermatous chronic GVHD among all surviving patients was higher (10.5%) than that previously reported (3.4-3.6%),[2,3] probably because of a higher incidence of chronic GVHD. In fact, the rate of scleroderma among patients with chronic GVHD was similar (14%) to that in other studies (13.2%).[2,3] The increasing use of unrelated donors and peripheral blood as the source of stem cells in allogeneic HSCT in recent years could be the cause of a higher incidence of chronic GVHD than that reported previously.[1-3] Our patients shared some clinical characteristics with those affected by systemic sclerosis and by autoimmune scleroderma-like syndromes.[2-4] Female predominance and Raynaud's phenomenon were not detected in our series, as in other series.[2,3] Lichenoid chronic GVHD did not always

Table 3. Univariate analysis of predictor variables for sclerodermatous chronic GVHD.

Variables	*At time of HSCT*		*At time of cGVHD*	
	HR (95% CI)	*p value*	*HR (95% CI)*	*p value*
Age at HSCT (years)				
≤28	5.7 (1.8-18.2)	0.003	6.6 (2-21)	0.001
> 28	1		1	
Sex				
Female	1.7 (0.6-4.7)	0.3	1.5 (0.5-4.4)	0.4
Male	1		1	
Phase				
Late	1.2 (0.4-3.6)	0.7	1 (0.3-3.2)	0.9
Early	1		1	
Donor				
Matched unrelated donor	3 (1.0-8.9)	0.04	2.7 (0.9-8)	0.06
Matched related donor	1		1	
HLA match				
No	5.5 (1.5-20.9)	0.01	4.4 (1.2-16)	0.03
Yes	1		1	
Sex match				
No	3.3 (0.9-11.9)	0.06	3.4 (1-12.4)	0.06
Yes	1		1	
Conditioning regimen				
TBI-based	2.1 (0.7-6.1)	0.2	2.1 (0.7-6.1)	0.2
Chemotherapy based	1		1	
Source of stem cells				
Peripheral blood	3.4 (1.2-10)	0.02	3.9 (1.3-11.9)	0.01
Bone marrow	1		1	
CD34 cell dose ($\times 10^6$/kg)				
>median of 2.7	2.7 (0.8-9.2)	0.1	2.9 (0.9-9.9)	0.08
≤median of 2.7	1		1	
CD3 cell dose ($\times 10^7$/kg)				
>3.9	7.5 (2.1-26.3)	0.002	7 (2-24.6)	0.002
≤3.9	1		1	
Acute GVHD (skin)				
Yes			1.5 (0.5-4.5)	0.45
No			1	
Chronic GVHD				
Extensive			4.9 (1.4-17.8)	0.01
Limited			1	
Chronic GVHD (skin)*				
Yes			3.7 (1.0-13.5)	0.04
No			1	
Chronic GVHD (skin-type)				
Disorders of pigmentation**			8.5 (2.2-32.5)	0.001
Lichenoid			1	
Chronic GVHD (mucosae)				
Yes			2.8 (0.8-9.9)	0.11
No			1	
Chronic GVHD (liver)				
Yes			3.2 (0.4-24.9)	0.2
No			1	
Chronic GVHD (lung)§				
Yes			1.2 (0.3-4.4)	0.8
No			1	
CMV Ag positive				
Yes			0.6 (0.2-2.6)	0.4
No			1	
DLI				
Yes			1.7 (0.5-6.2)	0.4
No			1	
Autoimmune markers				
Yes			11.2 (3-41)	0.0001
No			1	
Eosinophils (cells/μL)				
>500			10.8 (3.6-32.7)	<0.0001
≤500			1	
Lactate dehydrogenase (U/L)				
>500			7.1 (2.5-20.6)	0.0003
≤500			1	

*HR: hazard ratio; *: skin involvement by cGVHD before the onset of scleroderma; **: disorders of pigmentation such as hypo-hyperpigmentation and/or leopard skin eruption; §: lung involvement before the onset of scleroderma.*

precede the development of skin sclerosis, whereas it did in other studies.[2,6]

In our study, CD3 cell dose was significantly associated with the probability of developing sclerodermatous chronic GVHD in multivariate analysis at time of HSCT. Higher CD3 cell dose could facilitate subsequent immune hyperactivity and consequently a more severe form of chronic GVHD. At the time of chronic GVHD, disorders of pigmentation, development of eosinophilia and autoimmunity were significant predictors of the development of skin sclerosis. Increased levels of tumor necrosis factor-α (type cytokine) were found in hyperpigmented skin of patients with chronic GVHD[13] as well as in serum of patients with systemic sclerosis.[14] Eosinophilia has been previously associated with chronic GVHD and eosinophilic fasciitis, a scleroderma-like syndrome recently considered as a form of sclerodermatous GVHD.[4,7] Several studies reported a correlation between autoimmunity markers and chronic GVHD.[1,15,16] Autoantibodies are the expression of B-cell hyperactivity promoted by autoreactive T cells in autoimmune disease and by donor T cells in chronic GVHD.[14,16] Sato *et al.*[17] hypothesized that B-cell hyperactivity might not only be an epiphenomenon of T-activation but also a co-factor in the pathogenesis of fibrosis in systemic sclerosis. Patients with systemic sclerosis have increased numbers of naive B cells, chronic hyperactivity of memory B cells, and increased interleukin-6 production, which promotes the synthesis of collagen and extracellular matrix.[17] This model of a relationship between autoimmunity and skin fibrosis could be applied to sclerodermatous GVHD in view of the numerous immunological analogies with systemic sclerosis.[14,15,18] Eosinophilia and autoimmunity are expressions of Th-2 hyperactivity, and recent data have suggested that chronic GVHD may be a Th-2-mediated process.[1,7,16] On the other hand, there is clinical and experimental evidence of Th-1-hyperactivity in chronic GVHD, including in its sclerodermatous form.[4,16,18] It is not clear whether a Th-1 or Th-2 response prevails in chronic GVHD, particularly in the case of sclerotic changes, or whether both are involved at different times and may cause different clinical courses.[1,4,16,18] A comparison of survival curves suggested that, among cases with chronic GVHD, patients with scleroderma tended to have a poorer survival. Unlike previous studies,[2,3] in our experience patients with generalized scleroderma had a poorer outcome than had those with the localized form, probably because of lung involvement. Several therapeutic approaches (extracorporeal photochemotherapy, etretinate, CD20 and monoclonal antibodies to tumor necrosis factor-α and CD20, thalidomide and clofazimine) have been suggested for refractory sclerodermatous chronic GVHD.[1-3] We obtained encouraging results with methotrexate, wich we used because of its therapeutic indications for systemic sclerosis.[19] In conclusion, we observed a higher incidence (10.5%) of sclerodermatous chronic GVHD than that reported in previous studies. Disorders of pigmentation, eosinophilia and autoimmunity were significant predictors in multivariate analysis for the development of skin sclerosis in chronic GVHD and could have an immunological explanation. Since the small number of events of interest could have limited the statistical power of the multivariate analysis further studies involving larger numbers of patients would be useful to confirm our findings.

CS was the principal author responsible for the design of the study, the collection of the data and writing the paper. CS, FP and AS were responsible for the statistical analysis and interpretation of the data. MC, CF, FZ, RS and AG were involved in the design of the study, the collection and the interpretation of the data. FP, DD and RF gave the main contribution in the critical revision of the text.

We thank our colleagues of the Division of Dermatology (University Hospital of Udine) for their expert collaboration, and Paola Tonel and Stefano Martellos for their contribution to the revision of the text. This work was supported by A.I.L. (Associazione Italiana Leucemie).

Manuscript received August 21, 2005. Accepted December 12, 2005.

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