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Stem Cell Transplantation

Clinical grading of oral chronic graft-versus-host disease in 104 consecutive adult patients

The aim of this study was to investigate the clinical relevance of oral involvement by chronic graft-versus-host disease. The presence of oral changes in association with skin and other target organs including eye, lung or joint may adversely influence the probability of discontinuing systemic immunosuppressive treatment.

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The importance of oral manifestations of chronic graft-versus-host disease (GVHD) remains ill-defined and it might be surmised that selected patients with oral involvement may not require the aggressive immunosuppressive treatment (IST) that would naturally be used for extensive chronic GVHD. We evaluated the incidence and the clinical characteristics of oral chronic GVHD and investigated the impact of oral chronic GVHD on IST requirements, overall survival and non-relapse mortality (NRM). Between November 1990 and April 2001, 147 adult patients (median age 38 years, range 18-71 years) with hematologic malignancies who received a hematopoietic stem cell transplantation (HSCT), survived at least 100 days after HSCT and were at risk of chronic GVHD. Patients underwent HSCT from HLA-matched sibling donors (n=120), partially matched related donors (n=8) or matched unrelated donors (n=19). The anatomic areas of the oral cavity evaluated for assessment of involvement by chronic GVHD were the buccal mucosa (cheeks), tongue, lips and palate.

A modified model of the Oral Mucosal Rating Scale (OMRS)[1] was employed to quantify the extent and severity of oral mucosal involvement by chronic GVHD. Objective changes, including erythema, lichenoid and atrophy, were rated on scales ranging from 0 to 3 (0, normal; 1, mild; 2, moderate; 3, severe changes). Mild changes were defined as <25% involvement in one or more anatomic areas, moderate changes were defined as 25-50% involvement and severe changes as > 50% involvement. Ulceration and pseudomembrane formation were rated on scores based on estimated surface area involved (0, none; 1, >0 1 cm^2; 2, >1 cm^2 2 cm^2; 3,

Table 1. Characteristics of patients with oral chronic GVHD.

	Total (n=56)	*Mild/moderate oral involement (n=40)*	*Severe oral involement (n=16)*
Day of onset of oral chronic GVHD (range)	148 (76-925)	151 (76-925)	121 (78-290)
Clinical Manifestations			
Erythema	25 (44%)	20 (50%)	5 (31%)
Lichenoid Mucosal Changes	38 (68%)	29 (72%)	9 (56%)
Oral Atrophy	11 (19%)	1 (2%)	10 (62%)
Ulcerations & Pseudomembrane	15 (26%)	2 (5%)	13 (81%)
Sites			
Cheeks	55 (98%)	39 (97%)	6 (100%)
Tongue	17 (30%)	8 (20%)	9 (56%)
Lips	10 (18%)	7 (17%)	3 (18%)
Palate	9 (16%)	4 (10%)	5 (31%)
No. of sites involved			
1	28 (50%)	23 (57.5%)	5 (31%)
2	21 (37.5%)	16 (40%)	5 (31%)
3 - 4	7 (12.5%)	1 (2.5%)	6 (38%)
Symptoms			
Absent	30 (54%)	27 (68%)	3 (19%)
Dryness	14 (25%)	12 (30%)	2 (12.5%)
Difficulty in swallowing	9 (16%)	0	9 (56%)
Pain	3 (5%)	1 (2%)	2 (12.5%)
Other organs involved			
Localized skin	34 (61%)	26 (65%)	8 (50%)
Extensive skin	16 (28%)	10 (25%)	6 (37%)
Liver	19 (34%)	14 (35%)	5 (31%)
GI tract	9 (16%)	4 (10%)	5 (31%)
Eye	8 (14%)	5 (12%)	3 (19%)
Joint contractures	7 (12%)	4 (10%)	3 (19%)
Lung	4 (7%)	3 (7%)	1 (6%)
Mouth only	3 (5%)	2 (5%)	1 (6%)
Immunosuppressive therapy			
Local	1 (2%)	1 (2%)	0
Single systemic	17 (30%)	16 (40%)	1 (6%)
Double systemic	24 (43%)	17 (43%)	7 (44%)
Triple systemic	14 (225%)	6 (15%)	8 (50%)
Median duration of immunosuppressive therapy from onset of oral chronic GVHD (range)	589 (21-4167)	451 (21-3554)	1174 (41-4167)
Follow-up from transplantation, median days (range)	1792 (964-4374)	1666 (964-3840)	2262 (1013-4374)

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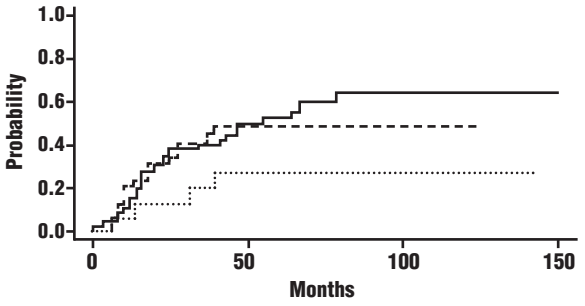

Figure 1. Time to discontinuation of systemic immunosuppressive therapy. The 3-year cumulative incidence of successful discontinuation of systemic IST was 39%, 41% and 19% for patients without oral involvement (solid line), patients with mild/moderate oral chronic GVHD (dashed line) and patients with severe oral changes (dotted line), respectively; (no oral chronic GVHD or mild/moderate vs severe oral chronic GVHD $p<0.05$).

>2cm^2). Overall, patients were categorized as having mild, moderate or severe oral chronic GVHD according to the single site with the worst score. Histologic documentation was not routinely performed. One hundred and four of the 147 (71%) patients developed chronic GVHD, which was graded as limited disease in 38 (37%) cases and extensive disease in 66 (63%) cases. The cumulative incidence of chronic GVHD at 6 months was 66.6% (95% CI, 66.3%-66.9%). Fifty-six patients (54%) had oral GVHD: 21 had mild, 19 had moderate and 16 had severe changes. The median time from the onset of chronic GVHD to the appearance of oral manifestations ranged from 5 to 775 days (median 68 days). The clinical characteristics of patients with oral chronic GVHD are summarized in Table 1. There was a non-significant trend toward prolonged administration of steroids among patients with severe oral chronic GVHD (median duration 273 days, range 9-3778) as compared to in those with mild/moderate oral involvement (median duration 166 days, range 14-1177; p=0.07). Interestingly, steroid-dependent chronic GVHD or refractory chronic GVHD requiring second-line treatments were more frequently observed in patients with severe oral chronic GVHD (10 patients, 62%) than in patients with mild/moderate oral involvement (7 patients, 17%) or those without oral changes (14 patients, 29%; p=0.004). The median duration of systemic IST from the onset of oral chronic GVHD was significantly longer in patients with severe oral involvement than in patients with mild/moderate oral involvement (p=0.01)(Table 1). The cumulative incidence of successful discontinuation of IST was 41% for patients with mild/moderate oral chronic GVHD as compared to 19% for patients with severe involvement (Figure 1). Multivariate analysis showed that multiorgan involvement (i.e. skin, mouth and eye ± lung ± joint contractures) was the only independent adverse prognostic factor for successful withdrawal of systemic IST (p=0.01), while a matched unrelated donor transplant was an independent adverse prognostic factor for NRM (p<0.001). Fatal infections were associated with mild/moderate oral chronic GVHD in 3 cases and in 1 case in patients with severe changes.

Several factors have been reported to be associated with poor prognosis in patients with chronic GVHD.[2-6] Nevertheless, to our knowledge only the study by Lee *et al.*[7] recognized oral involvement in association with high Karnofsky performance score as favorable prognostic signs, and skin involvement, diarrhea and weight loss as unfavorable factors.

Two major conclusions can be drawn from our study. First, the oral mucosa is frequently involved by the process of chronic GVHD: overall, 54% of the patients included in our series had clinically evident oral chronic GVHD. This rate is roughly the same as that reported in other studies.[4,7-9] Second, it is important to have an objective assessment of oral lesions to measure their severity; infact, patients with severe oral involvement in association with involvement of other target organs (skin and eye ± lung ± joint) may require intensive and prolonged immunosuppressive treatments. In the light of these considerations, clinical grading of oral chronic GVHD may be useful in allogeneic HSCT. It can be hypothesized that oral chronic GVHD may benefit from treatments tailored by rating the severity of mouth involvement.

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Stem Cell Transplantation

Cytomegalovirus infection and chronic graft-versus-host disease are significant predictors of renal failure after allogeneic hematopoietic stem cell transplantation

We investigated the frequencies and predictive factors of prolonged renal failure (PRF) in a retrospective study of 181 consecutive patients undergoing allogeneic hematopoietic stem cell transplantation. Twenty-six patients (23% of long-term survivors) developed PRF. We identified 4 independent prognostic factors; cytomegalovirus infection and chronic graft-versus-host disease appeared as major risk factors for PRF.

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From 5 to 20% of long-term survivors of allogeneic hematopoietic stem cell transplantation (HSCT) develop late renal failure.[1-5] Predictive factors of renal dysfunction have not been firmly established.[1,6-8] Consecutive patients undergoing allogeneic HSCT in a single institution during ten years were retrospectively studied to determine frequencies and predictive factors of prolonged renal failure (PRF) and chronic renal failure (CRF).

One hundred and eighty-one adult patients, transplanted in the Hematology Unit of Besançon university hospital from January 1990 to December 1999, were included. The most frequent indication for transplantation was acute leukemia, in complete remission in 74% of the cases. All patients were conditioned with a myeloablative regimen, with total body irradiation (TBI) (12 Gy fractionated in 6 doses every 12 hours, with no renal shielding) in 132 cases (Table 1). Graft-versus-host disease (GVHD) prophylaxis comprised cyclosporine (Cs-A) in all but four cases (98%); Cs-A was administered intravenously during the first 3 weeks and adjusted following weekly assays; administration was continued orally at full dose for 3 months and then progressively tapered (10% reduction every week) to be finally stopped 6 months after transplantation in the absence of GVHD. All patients received low-dose heparin to prevent veno-occlusive disease.[9] Creatinine clearance was calculated according to the Cockcroft and Gault formula; PRF was defined by a creatinine clearance remaining under 50 mL/min for at least 6 months, followed by subsequent recovery. CRF was defined by a creatinine clearance remaining under 50 mL/min for at least 12 months without further improvement.

The statistical end-point was PRF; the definitions used for PRF did not allow analyses including observation time or the cumulative incidence and competing risks. By definition analysis was restricted to patients surviving at least 6 months post-transplantation. A logistic regression analysis was chosen to analyze the relation between renal failure and the relevant covariates.

Table 1. Characteristics of the patients and transplants.

Parameter	*Number (%)*
Age (years), Median [Range]	36 [15 - 62]
Sex ratio (Male/Female)	108/73 (60/40)
Diagnosis (pts/%)	
Acute myeloblastic leukemia	50 (28)
Acute lymphoblastic leukemia	43 (24)
Chronic myeloid leukemia	37 (20)
Non-Hodgkin's lymphoma	26 (14)
Myelodysplasia	15 (8)
Myeloma	3 (1.5)
Hodgkin's disease	2 (1)
Other	3 (1.5)
Donor-recipient compatibility (pts/%)	
Identical twins	2 (1)
Related partial match or matched sibling	149 (82)
Unrelated	30 (16)
Conditioning regimen (pts/%)	
Containing TBI*/Containing Cy†	132 (73)/116 (64)
Cy† - TBI*	91 (50)
Bu‡-Cy†/Bu‡-Mel§/Bu‡-Ara-C@	22 (12)/21(12)/34(19)
Other	39 (21)
Previous BMT (pts/%)	28 (15)
Autologous	23 (13)
Allogeneic	5 (3)
Containing TBI	19 (83)
Survival¶	
Median survival time (months)[range]	18 [0.5-128]
5-year survival	42±3%
7-year survival	39±4%

**TBI: total body irradiation; †Cy: cyclophosphamide; ‡Bu: busulfan; §Mel: melphalan; @Ara-C: cytarabine; ¶The occurrence of acute renal failure or PRF had no significant impact on survival after HSCT.*

Seventy-nine patients (44%) were long-term survivors with a median follow-up of 52 months (12-128) post-transplantation; 124 patients (68%) developed acute renal failure. PRF was diagnosed in 26 patients (23% of those surviving more than 6 months); 5 of them recovered a normal creatinine clearance after 6 months of renal insufficiency. Ten patients, 38% of the patients with PRF and 11% of those surviving more than one year, still had altered renal function at that time and were classified as having CRF. No patient developed CRF without previous acute renal failure or PRF. One patient with CRF still required dialysis 5 years after HSCT. A few factors had a significant impact on PRF in univariate analysis: male sex, response status after transplantation, the number of days of Cs-A exposure and the presence of chronic GVHD, hypertension or

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