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Mucositis after Allogeneic Hematopoietic Stem Cell Transplantation: A Cohort Study of Methotrexate- and Non–Methotrexate-Containing Graft-versus-Host Disease Prophylaxis Regimens

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ABSTRACT

Oral mucositis occurs in up to 75% of recipients of high-dose chemoradiotherapy conditioning regimens used for allogeneic hematopoietic stem cell transplantation (HSCT). As a result of mucositis, narcotic analgesia and total parenteral nutrition (TPN) are commonly required after HSCT. Methotrexate, an antiproliferative graft-versus-host disease (GVHD) prophylaxis agent, impairs mucosal regeneration and worsens and prolongs mucositis. We assessed the effect of substituting sirolimus for methotrexate as GVHD prophylaxis on outcomes associated with mucositis. Two patient cohorts undergoing allogeneic HLA-matched related donor peripheral blood stem cell transplantation with cyclophosphamide/total body irradiation conditioning were prospectively analyzed for mucositis severity and retrospectively reviewed for correlative outcomes. GVHD prophylaxis consisted of sirolimus/tacrolimus (ST) in the study group and tacrolimus/methotrexate (TM) in the control group. Thirty patients received ST and 24 patients received TM as GVHD prophylaxis between October 2000 and May 2003. Mild, moderate, and severe mucositis was noted in 37%, 57%, and 7% of the ST group and 8%, 42%, and 50% of the TM group (P = .0002). Less TPN was used in the ST group than the TM group (17% versus 43% of posttransplantation hospital days; P = .02). The total number of narcotic days was lower in the ST group in comparison with the TM group (median, 13.5 versus 17 days; P = .08). The time to first hospital discharge was shorter in the ST group compared with the TM group (median, 18 versus 22 days; P = .07). The substitution of sirolimus for methotrexate as GVHD prophylaxis is associated with a reduction in mucositis severity. As a result, TPN and narcotic use are reduced, and hospitalization duration is shortened. Less toxic GVHD prophylaxis regimens without methotrexate may have a significant effect on patient quality of life, patient outcomes, and economic outcomes associated with allogeneic stem cell transplantation.

KEY WORDS

Oral mucositis • Sirolimus • Stem cell transplantation

INTRODUCTION

Mucositis is a frequent complication of high-dose chemoradiotherapy regimens commonly used as conditioning therapy before allogeneic hematopoietic stem cell transplantation (HSCT). Oral mucositis occurs as a result of chemotherapy- and radiotherapy-induced mucosal epithelial injury, submucosal endothelial injury, and connective tissue injury in an immunocompromised host. [1] Severe oral mucositis occurs in up to 75% of myeloablative allogeneic HSCT recipients, often occurs within the first week

after conditioning therapy, and usually resolves only when normal hematopoiesis resumes. [2]

Oral mucositis is a significant problem for most HSCT recipients and has been reported to be the most debilitating side effect of transplantation. [3,4] Mucositis has immediate detrimental effects on patient quality of life by causing oral and oropharyngeal pain and by impairing communication and swallowing. As a result of pain related to mucositis, narcotic analgesia and parenteral nutrition are commonly required in the recovery period after HSCT. In addition, oral mucositis is associated with adverse economic and clinical outcomes after HSCT, including an increased length of hospital stay and decreased survival at 100 days. [5] Although several attempts at preventing, minimizing, and treating mucositis after allogeneic stem cell transplantation have been made, no single therapy has been shown to be effective in randomized clinical trials, and the current standard therapy for mucositis is supportive care alone. [6,7]

Although conditioning therapy is the most important cause of mucositis after allogeneic HSCT, the contribution of methotrexate as graft-versus-host disease (GVHD) prophylaxis cannot be overlooked. As an antiproliferative agent, methotrexate impairs mucosal regeneration after conditioning-related injury, thereby prolonging and worsening oral mucositis. The risk of mucositis is particularly increased among methotrexate recipients who carry the methylenetetrahydrofolate reductase 677 TT genotype, because of imbalances in intracellular folate pools. [8]

At the Dana-Farber Cancer Institute, we have performed several clinical trials to assess the efficacy of sirolimus, a novel immunosuppressive agent, as GVHD prophylaxis when given in addition to or in lieu of methotrexate. [9,10] Herein, we report a retrospective cohort analysis comparing outcomes related to mucositis in patients who received a sirolimus-based, methotrexate-free GVHD prophylaxis regimen with outcomes in patients who received a methotrexate-containing regimen.

METHODS

Experimental Design

This was a cohort analysis examining oral mucositis outcomes of patients undergoing allogeneic peripheral blood stem cell transplantation from HLA-matched, related donors for hematologic malignancies. Two cohorts of patients were prospectively evaluated for the oral mucositis outcomes of interest. Oral mucositis was assessed prospectively at the time of transplantation, and the associated outcomes were assessed retrospectively.

The experimental cohort consisted of 30 consecutive patients who underwent matched related donor allogeneic peripheral blood stem cell transplantation by using a novel GVHD prophylaxis regimen. Details on this experimental protocol have been previously published. [10] Briefly, patients received myeloablative conditioning therapy with cyclophosphamide (1800 mg/m^2/d for 2 days) and total body irradiation (14 Gy in 7 fractions) before peripheral blood stem cell transplantation. GVHD prophylaxis consisted of sirolimus and tacrolimus (ST). No posttransplantation methotrexate was given.

The control population consisted of all other patients who underwent matched related donor peripheral blood stem cell transplantation at the Dana-Farber Cancer Institute with an identical conditioning regimen, but with the standard GVHD prophylaxis regimen of tacrolimus and methotrexate (TM; 15 mg/m^2 day +1 and 10 mg/m^2 days +3, +6, and +11). Twenty four patients were identified as suitable controls. No patient had had prior high-dose chemotherapy with stem cell support therapy. All subjects participated in institutional review board–approved protocols allowing collection and analysis of data from transplantation.

Mucositis Assessment

Patients were prospectively assessed thrice weekly by trained and validated evaluators from the Oral Medicine Service of Brigham and Women's Hospital as part of routine clinical care. Oral evaluators were not blinded to GVHD prophylaxis assignment. The severity of oral mucositis was assessed by using a validated scale in which the presence of mucosal erythema or ulceration was determined for 8 predefined anatomic locations in the oral cavity. [11] A mucositis score of 0 connotes normal oral mucosa; 1 indicates the presence of erythema only; 2 and 3 reflect the presence of ulceration of 1 or 2 sites, respectively (slight to moderate mucositis); and 4 (3 ulcerative sites) or 5 (>3 sites of ulceration) is consistent with severe mucositis.

Information on the use and duration of use of total parenteral nutrition (TPN) and narcotics, as correlates of oral mucositis, was collected by a retrospective chart review. Narcotic use was obtained from electronic pharmacy dispensation records. Narcotics were converted to morphine equivalents by using published narcotic conversion tables. [12]

Statistical Analysis

Descriptive statistical analyses were performed to compare demographic characteristics, including age, sex, donor type, malignant disease, and disease status at the time of transplantation. Time to engraftment was measured by cumulative incidence. The Cochrane-Mantel-Haenszel statistic was used to compare the severity of oral mucositis (mild, moderate, and severe) between

Table 1. *Baseline Characteristics*

Variable	Sirolimus/Tacrolimus	Tacrolimus/Methotrexate	*P* Value
Sample size	**30**	**24**	
Median age, y (range)	**42 (19-54)**	**43 (24-58)**	**.46**
Male sex	**16 (53%)**	**11 (46%)**	**.78**
Hematologic malignancy			
AML	**10 (33%)**	**9 (38%)**	
CML	**7 (23%)**	**3 (13%)**	
NHL	**7 (23%)**	**3 (13%)**	
MDS	**5 (17%)**	**7 (29%)**	
ALL	**1 (3%)**	**2 (8%)**	**.52**
Days to neutrophil engraftment (range)	**14 (11-17)**	**15 (11-25)**	**.04**
Grade II-IV acute GVHD	**3 (10%)**	**6 (25%)**	**.16**

No significant differences in baseline characteristics were observed between treatment groups, with the exception of the time to neutrophil engraftment.

AML indicates acute myelogenous leukemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; ALL, acute lymphatic leukemia.

the 2 groups. A 2-sided Wilcoxon rank sum test was used for the comparison of duration of oral mucositis, days and doses of narcotics administered, time from transplantation to first hospital discharge, and days of TPN use with and without adjustment for the difference in total hospital days between groups. A 2-sided Fisher exact test was used to compare GVHD incidence, TPN use, and the incidence of severe oral mucositis.

RESULTS

The demographic and transplantation characteristics of patients in this study are shown in Table 1. All patients received peripheral blood stem cells from HLA-matched related donors. There were no statistical differences between the 2 groups when age, sex, hematologic malignancy, and the incidence of acute (grade II-IV) GVHD were examined. The ST group engrafted neutrophils (>500/μL) 1 day earlier in comparison to the TM group (14 versus 15 days; $P = .04$).

Mucositis

Screening for mucositis occurred with equal frequency for ST and TM patients (median, 5 versus 6.5 times; $P = .36$). Peak mucositis scores are shown in Table 2. Oral mucositis was less severe in the ST group than in the TM group ($P = .0002$; Figure 1). The incidence of severe, ulcerating (grade 4/5) mucositis was lower in the ST group (50% versus 6.7%; $P < .001$). The median number of days with mucositis (≥2) among the entire ST group was reduced when compared with the TM group (median, 4.5 versus 9.5 days; $P = .008$; Figure 1). However, among patients with mucositis, the median number of days with a mucositis score ≥2 (median, 8 versus 12 days; $P = .19$), ≥3 (median, 5 versus 9 days; $P = .11$), and ≥4 (median, 10 versus 8 days; $P = 1.00$) was similar between the ST and TM groups. There was no correlation between time to engraftment and peak mucositis score. Four individuals in the TM group engrafted on or after day 21. These 4 individuals all had peak mucositis scores >2, and 2 individuals experienced grade 4 or 5 mucositis.

Table 2. *Incidence of Oral Mucositis by Severity*

Variable	Peak Mucositis Score		
	0/1	2/3	4/5
Sirolimus/tacrolimus	**11 (37%)**	**17 (57%)**	**2 (7%)**
Tacrolimus/methotrexate	**2 (8%)**	**10 (42%)**	**12 (50%)**

$P = .0002$.

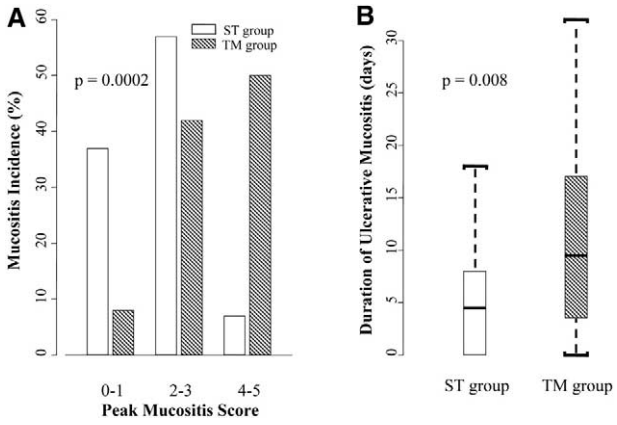

Figure 1. Mucositis incidence and duration. A, Peak mucositis scores were significantly lower in the ST group. B, Boxplot demonstrating differences in mucositis duration. The limits of the box represent the 25th and 75th percentiles for the group, the solid line in the center of the box represents the median for the group, and the tails arising out of the box represents the range that includes 95% of observed values. Duration of mucositis ≥2 was also significantly shorter. A mucositis score of 0 connotes normal oral mucosa; 1 indicates the presence of erythema only; 2 and 3 reflect the presence of ulceration of 1 or 2 sites, respectively (slight to moderate mucositis); and 4 (3 ulcerative sites) or 5 (>3 sites of ulceration) is consistent with severe mucositis.

Narcotic Use

The total number of hospital days when narcotics were used as pain control was lower in the ST group (median, 13.5 versus 17 days; $P = .08$; Figure 2). The total dose of narcotics administered is expressed as intravenous milligrams of morphine equivalents (MME). Patients in the ST arm received an average of 880 MME, in comparison to 1225 MME in the control arm (Figure 2). Similarly, patients in the ST group used fewer MME per hospital day than the TM arm (median, 41.2 versus 61.7 MME per day; Figure 2) and fewer MME per narcotic day (median, 61.9 versus 95.2 MME per narcotic day; Figure 2). None of these results achieved statistical significance.

Total Parenteral Nutrition

The median number of days of TPN use in the ST arm was significantly lower than in the TM group (2 versus 14 days; $P = .005$; Figure 3) and was shorter even when controlling for the total number of posttransplantation hospital days (17% versus 43% of posttransplantation hospital days; $P = .02$). A smaller proportion of patients in the ST group required any TPN (50% versus 75%; $P = .06$), and among the users of TPN, the duration of TPN was significantly shorter (13 versus 17.5 days; $P = .03$).

Length of Hospital Stay

Patients who received ST had a shorter length of hospitalization from the time of transplantation when compared with the TM group (median length of stay, 18 versus 22 days; $P = .07$; Figure 4).

DISCUSSION

In this retrospective cohort analysis, we have demonstrated that the use of a sirolimus-based, non–methotrexate-containing GVHD prophylaxis regimen is associated with a decrease in the incidence and severity of oral mucositis after HLA-matched related donor peripheral blood stem cell transplantation. In addition, mucositis-related outcomes, such as TPN use, narcotic use, and hospitalization duration, are also improved when a nonmethotrexate GVHD prophylaxis regimen is used. To date, 1 other trial has demonstrated a decrease in mucositis and mucositis-related outcomes when methotrexate was replaced in the GVHD prophylaxis strategy. [13] Another GVHD prophylaxis strategy used to diminish mucositis is reduced-dose methotrexate; however, mucositis outcomes with this approach have not been formally evaluated.

Strategies used to prevent or reduce oral mucositis after allogeneic stem cell transplantation have included strict oral hygiene, [14] glutamine supplementation, [15,16] topical and systemic hematopoietic growth fac-

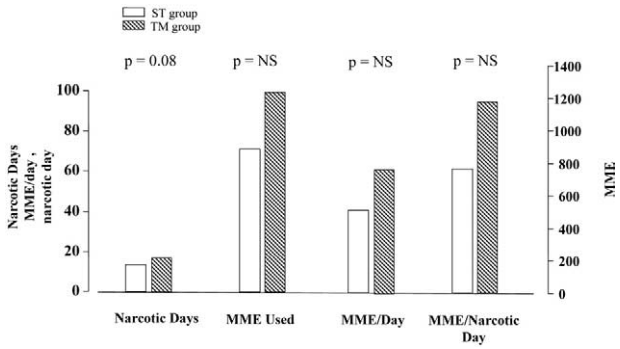

Figure 2. Narcotic use. Patients in the ST group received narcotics on fewer days after transplantation ($P = .08$). There was a trend to decreased total milligrams of morphine equivalents (MME) used after transplantation. When standardized to posttransplantation days or posttransplantation days when any narcotic was administered, the trend to fewer MME remained. NS indicates not significant.

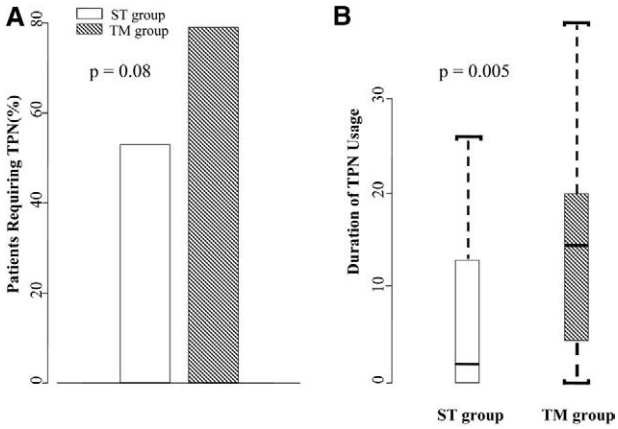

Figure 3. TPN use and duration of use. A, Less TPN was used in the ST group ($P = .08$). B, The duration of TPN use was significantly shorter in the ST group ($P = .005$).

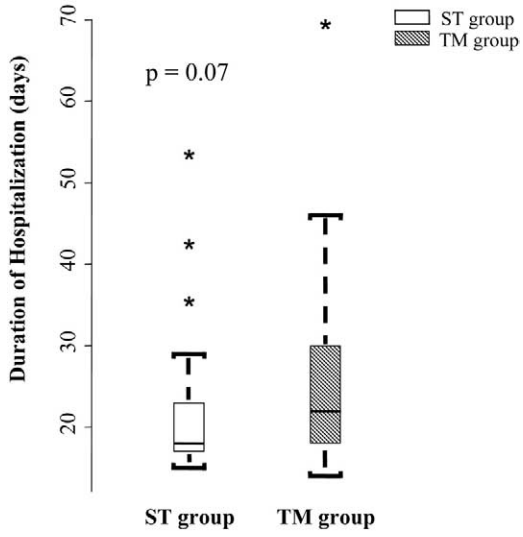

Figure 4. Duration of hospitalization: the hospitalization duration was 4 days shorter from the time of transplantation in the ST group.

tors, [17-20] interleukin 11, [21,22] and bacterial decontamination of the oral cavity. [23] Although some of these strategies yielded promising results, none is widely accepted as standard therapy. Several newer agents may have a potential role in the prevention of oral mucositis, including the protegrin-1-analog-iseganan [24] and fibroblast growth factor 20, [25] although the clinical development of iseganan has now been abandoned. Palifermin, a keratinocyte growth factor analog, has shown the most promise. In a randomized phase III study conducted in patients undergoing autologous transplantation, the incidence of World Health Organization grade 3/4 mucositis was reduced from 98% to 63% ($P < .001$), and the incidence of World Health Organization grade 4 mucositis was reduced from 62% to 20% ($P < .001$). [26] In addition, palifermin use was associated with an improved quality of life of patients undergoing stem cell transplantation [27] and with favorable economic outcomes. [28]

In our observational study, we observed clinical benefits similar to those seen in the palifermin trial, with similar reductions in narcotic use and TPN use. The hospitalization duration was shortened by 4 days when the nonmethotrexate and methotrexate cohorts were compared. Although this result was not statistically significant, likely because of the small sample size, a difference of 4 days is clinically relevant. Much of this difference could be attributable to the more rapid engraftment seen in the nonmethotrexate cohort; however, the timing of discharge in relation to engraftment is often based on the reinstitution of normal oral intake, which is related in part to oral mucositis. With hospitalization costs that exceed $150 000 for traditional, non–T cell–depleted transplantation, [29] this reduction in hospital stay alone may amount to significant cost savings for transplantation programs and insurers. However, when the reductions in TPN and narcotic use are added, the cost savings associated with prevention of ulcerative mucositis may be associated with a savings of more than $42 000 per hospital stay. [5] These cost savings, however, may be offset by the increased costs associated with sirolimus use, which in this study was administered for at least 100 days after transplantation. The true cost-benefit outcomes of this strategy, incorporating the costs of prophylaxis and therapy of GVHD, are the subject of a formal cost-efficacy analysis.

It has been demonstrated that chemotherapy patients who do not experience mucositis have a decreased incidence of mood disturbance compared with those who experience mucositis. [30] Although mood disturbance is an important measure of quality of life, it is likely to be only 1 of many contributing factors. Quality of life in the immediate posttransplantation period is very difficult to ascertain, and alterations in quality of life are difficult to ascribe to single-system problems because of the inherent multifactorial nature of posttransplantation complications. Therefore, when trying to consider oral mucositis outcomes alone, it is difficult to determine what are the clinically important end points. One attempt to address this issue has been the use of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, with the oral addendum module. [31] The oral mucositis patient provider advisory board has suggested that reductions in oral pain, opioid analgesic use, and hospitalization duration are among the important markers. [32] Because we have demonstrated improvements in all 3 of these domains, it is likely that the substitution of sirolimus for methotrexate in the GVHD prophylaxis regimen is associated with an improvement in quality of life in the immediate posttransplantation time period.

It is likely that very little bias influenced the analyses reported here. Although the trained oral observers were not blinded to GVHD prophylaxis, the nature of this observational study was unknown to them, and their examinations were part of routine clinical care. Similarly, clinicians caring for the patients in this study could have based decisions to implement parenteral nutrition biased by GVHD prophylaxis. However, the recommendations to institute parenteral nutrition were generally made by a nutritionist specializing in the care transplantation patients who was unaware of this observational study.

In summary, when compared with methotrexate-containing GVHD prophylaxis regimens after HLA-matched related donor peripheral blood stem cell transplantation, the use of a sirolimus-based regimen is associated with improved mucositis and mucositis-associated outcomes. Given only a 1-day difference in the time to engraftment between cohorts examined, it is likely that the methotrexate contributed directly to mucositis in this study. GVHD strategies that reduce or eliminate methotrexate from the GVHD prophylaxis regimen should be pursued to improve mucositis and mucositis-related outcomes after allogeneic transplantation, as long as GVHD control is not compromised. As such, a randomized clinical comparing the combinations of ST with TM will be performed. Although GVHD is the primary focus of this trial, mucositis outcomes will be important secondary end points.

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