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Mammalian Target of Rapamycin Inhibitor–Associated Stomatitis in Hematopoietic Stem Cell Transplantation Patients Receiving Sirolimus Prophylaxis for Graft-versus-Host Disease

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The mammalian target of rapamycin (mTOR) inhibitor sirolimus is effective in reducing incidence of graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). Agents that inhibit the mTOR pathway are known to be associated with significant and potentially dose-limiting toxicities, including stomatitis. The objective of this study was to report the clinical features and management outcomes of sirolimus-associated oral ulcers in the context of post-HSCT prophylaxis of GVHD. Seventeen patients, from a study cohort of 967, who were treated with sirolimus as prophylaxis for GVHD after allogeneic HSCT at the Dana-Farber/Brigham and Women's Cancer Center developed oral ulcers and were referred to the oral medicine clinic for evaluation and treatment over a period of 6 years. Clinical characteristics (appearance, anatomic site, size) and therapeutic outcomes (time to complete resolution) were documented. Median time to onset of oral ulceration was 55 days after allogeneic HSCT (range, 6 to 387 days); 92.9% of ulcers were located on nonkeratinized mucosa, with the ventrolateral tongue the most common site of involvement. Thirteen patients were treated with topical corticosteroid therapy; 12 of these patients also required intralesional corticosteroid injections. Clinical improvement (resolution of the lesions and improvement of symptoms) was noted in all cases, with no reported adverse events. Median time to complete resolution after onset of therapy was 14 days (range, 2 to 70 days). Patients receiving sirolimus for GVHD prophylaxis may develop painful oral ulcerations, which can be effectively managed with topical steroid treatment. Further prospective studies are needed to better elucidate the incidence of this complication, identify risk factors, and evaluate the effectiveness of interventions.

INTRODUCTION

Sirolimus (Rapamune, Pfizer, Princeton, NJ) is a mammalian target of rapamycin (mTOR) inhibitor with immunosuppressive properties [1]. Sirolimus binds uniquely to FK-binding protein 12 and forms a complex with mTOR, which inhibits the PTEN/PI3K/Akt and JAK pathways [2,3], resulting in downregulation of IL-2 and IL-15 signaling and reduced T and B lymphocyte proliferation [4-6]. Sirolimus has been widely used to prevent graft rejection in solid organ transplantation [7,8]. In renal transplantation, sirolimus-containing prophylaxis regimens have demonstrated advantages compared with azathioprine with respect to both decreasing the incidence and severity of rejection episodes, as well as improvement in graft function [9]. More recently, sirolimus has demonstrated efficacy in preventing and managing graft-versus-host-disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT) [4,10-12]. The substitution of sirolimus for methotrexate combined with a calcineurin inhibitor (tacrolimus) has demonstrated similar effectiveness for GVHD prophylaxis and a significantly reduced incidence and severity of methotrexate-associated toxicity, including oral mucositis [11,12].

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Sirolimus has a unique toxicity profile, with the most common side effects including hyperlipidemia, cytopenias, impaired wound healing, interstitial pneumonitis, acneiform rash, and aphthous-like oral ulcers [13-18]. The aphthous-like oral ulcerations have been observed in several clinical trials of sirolimus in renal transplantation, with an incidence rate of up to 60% [17,19-21]. These oral mucosal ulcers present as solitary or multiple lesions with rapid onset after initiation of sirolimus therapy and are characterized by a typical ovoid shape with a central gray area surrounded by an erythematous halo, affecting almost exclusively the non-keratinized mucosa [22]. The lesions can be sufficiently painful and debilitating to require discontinuation of sirolimus and substitution with an alternative immunosuppressive agent [20]. Although this complication has been well described in the context of solid organ transplantation, no data are available on sirolimus-associated oral ulcers presenting in the context of GVHD prophylaxis in HSCT. The objective of this study was to characterize the clinical features and management outcomes of sirolimus-associated oral ulcers in patients undergoing allogeneic HSCT with sirolimus-containing GVHD prophylaxis regimens.

METHODS

A retrospective case record review was conducted of all patients at Dana-Farber/Brigham and Women's Cancer Center between March 2006 and October 2012 who underwent allogeneic HSCT and received sirolimus for GVHD prophylaxis (n = 967) and who developed symptomatic aphthous-like oral mucosal lesions (typically round or ovoid with well-demarcated borders and focal perilesional erythema) that required intervention. This study was approved by the Dana-Farber/Harvard Cancer Center's Office for Human Research Subjects.

All patients for whom records were reviewed had been referred to the oral medicine practitioner (N.T.) by their transplantation oncologist for diagnosis and management of painful oral ulcerations. Clinical diagnosis of the oral mucosal lesions was based on characteristic aphthous-like features, including shallow ovoid ulcers with perilesional erythema, largely restricted to the unattached non-keratinized oral mucosa [18]. An incisional biopsy was obtained in 5 patients to rule out other mucosal pathology. Despite all patients receiving post-HSCT acyclovir prophylaxis, herpes simplex virus culture was obtained in all cases to rule out breakthrough recrudescence.

Electronic medical records and high-resolution digital photographs were reviewed, and data were collected using a standardized collection form and entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA). Data were collected based on the following 5 categories: (1) transplantation demographics (eg, diagnosis, conditioning regimen, and GVHD prophylaxis), (2) relevant indicators of medical status at time of onset of oral ulcers (eg, absolute neutrophil count, immunosuppressive medication regimen, sirolimus dose, and serum levels), (3) clinical parameters of the initial oral ulcer episode (eg, time to onset, oral sites affected, and severity), (4) clinical trajectory of the most persistent ("sentinel") lesion, and (5) management and time to complete resolution. Descriptive statistical analyses (medians, ranges, and totals) were performed using STATA, version 9.2 (Stata Corp, College Station, TX). Linear regression was used to explore the associations between sirolimus level and the number, severity, and/or duration of oral ulcers. All P values were considered to be statistically significant at $P < .05$.

RESULTS

Patient Characteristics

This study included 17 patients with a median age of 58 years (range, 28 to 66 years) (Table 1). All study patients underwent allogeneic HSCT at Dana-Farber/Brigham and Women's Cancer Center for management of underlying hematologic malignancies, with the majority receiving reduced-intensity conditioning regimens (15 of 17; 88.2%) and matched unrelated donor stem cell grafts (15 of 17; 93.8%). All patients received a combination of sirolimus and tacrolimus for GVHD prophylaxis beginning on day -3. Tacrolimus was initiated at a dose of .02 mg/kg/day by continuous intravenous infusion, adjusted to maintain a serum concentration of 5 to 10 ng/mL. Sirolimus was initiated with a 12 mg oral loading dose, followed by a daily oral dose of 4 mg, adjusted to maintain a serum trough concentration of 3 to 12 ng/mL.

Four patients reported a prior history of infrequent (ie, less than 6 ulcers per year) recurrent aphthous stomatitis. One patient developed conditioning regimen-associated oral mucositis that had fully resolved and healed before the onset of aphthous-like oral ulcers. None of the patients presented with GVHD at the time of onset of oral ulcers. Six patients developed acute GVHD. Eight patients developed systemic

Table 1
Patient Characteristics

Patient	Age	Gender	Diagnosis	Conditioning	Stem Cell Source	Matching	aGVHD	Time of Onset after HSCT, d	Maximum aGVHD Grade	cGVHD	Time of Onset after HSCT, d	cGVHD Organ Involvement
1	54	M	AML	RIC	BM	MUD	–		0	+	181	n/a
2	54	M	CLL	RIC	UCB	MUD	–		0	–		
3	58	F	NHL	RIC	UCB	MUD	–		0	–		
4	58	M	NHL	MAC	UCB	MUD	–		0	–		
5	61	M	MDS	RIC	PBSC	MUD	–		0	–		
6	36	F	CLL	RIC	PBSC	MMUD	+	n/a	3	+	189	Skin, eyes, mouth
7	59	M	AML	RIC	UCB	MUD	–		0	+	209	n/a
8	64	M	NHL	RIC	UCB	MUD	+	30	1	–		
9	28	M	CVID	RIC	PBSC	MUD	+	65	3	–		
10	51	F	MM	RIC	PBSC	MUD	+	44	2	+	313	Skin, mouth
11	65	M	CLL	RIC	PBSC	MUD	+	71	2	+	209	Skin, eyes, mouth
12	60	F	CLL	RIC	PBSC	MUD	+	103	2	–		
13	37	M	MDS	RIC	UCB	MUD	–		0	–		
14	65	M	NHL	RIC	PBSC	MUD	–		0	+	22	Skin, eyes, mouth, lung, liver, musculoskeletal, hematologic, soft tissue
15	55	M	MDS	RUC	PBSC	MUD	–		0	–		
16	41	F	AML	RIC	UCB	N/A	–		0	+	157	Skin, eyes, mouth
17	66	M	CLL	RIC	PBSC	MUD	–		0	+	216	n/a

aGHVD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; M, male; AML, acute myelogenous leukemia; RIC, reduced-intensity conditioning; BM, bone marrow; MUD, matched unrelated donor; n/a, not available; CLL, chronic lymphocytic leukemia; UCB, umbilical cord blood; F, female; NHL, non-Hodgkin lymphoma; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; PBSC, peripheral blood stem cells; MMUD, mismatched unrelated donor; CVID, common variable immunodeficiency syndrome; MM, multiple myeloma.