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LETTER TO THE EDITOR

Sirolimus-Related Toxicity in Stem Cell Transplantation

We read with interest the recently published article by Johnston et al., [1] which evaluated the efficacy and safety of sirolimus in combination with calcineurin inhibitors and steroids for the treatment of chronic graft-versus-host disease (cGVHD). The study indicates that sirolimus in conjunction with calcineurin inhibitors has activity in the treatment of cGVHD, although 37% of the patients developed severe toxicity (grade 3-4; National Cancer Institute Common Toxicity Criteria).

Here we report our retrospective analysis on the use of sirolimus in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Between February 2003 and December 2004, 15 patients receiving an allogeneic HSCT from HLA-identical siblings (n = 10), partially matched related donors (n = 2), or matched unrelated donors (n = 3) were given sirolimus. The immunosuppressant was introduced because of refractory cGVHD (n = 2) or calcineurin inhibitor–related toxicity (n = 13); this included renal insufficiency in all cases. Two patients had additional toxicity, including hepatic toxicity (n = 1) and thrombotic microangiopathy (n = 1). In patients with a history of calcineurin inhibitor toxicity, sirolimus was introduced as a GVHD prophylactic regimen (n = 9) or GVHD treatment (n = 4) in an attempt to taper off the calcineurin inhibitor. Sirolimus was initiated at 2 mg/d in 5 patients and 4 mg/d in 6 patients. This was targeted to maintain sirolimus trough concentrations of 5 to 15 mg/dL; 4 patients received sirolimus orally at a loading dose of 6 mg, followed by a maintenance dose of 2 mg/d. The median time to start sirolimus was 49 days (range, 10-5760 days) after transplantation (Table 1). Patients were treated with sirolimus in addition to steroids (n = 2), calcineurin inhibitors and steroids (n = 3), mycophenolate mofetil (MMF; n = 2), MMF and calcineurin inhibitor (n = 4), and MMF and steroids (n = 3); 1 patient received sirolimus alone. Thrombocytopenia (platelets <50 000/μL) was the most common adverse event, occurring in 9 (60%) patients. In 3 cases, thrombocytopenia was associated with the presence of platelet autoantibodies. In 5 patients, the number of platelets normalized after either removal of or reduction in the dose of sirolimus. Neutropenia (absolute neutrophil count <1000/μL) was noted in 6 (40%) patients. Three patients had complete resolution of neutropenia after the administration of granulocyte colony-stimulating factor; in 2 patients, the absolute neutrophil count normalized with no dose modification of sirolimus. One patient had persistent neutropenia even after discontinuation of sirolimus and required a second marrow graft. Renal insufficiency occurred in 5 (33%) patients.

Because 13 of 15 patients had a history of nephrotoxicity, for the purposes of this study, sirolimus-related renal toxicity was defined as an increase of creatinine levels ≥65% times baseline (ie, the value of creatinine before the first dose of sirolimus) with creatinine levels ≥2.0 mg/dL. The median time to develop renal toxicity was 30 days (range, 4-73 days) after the introduction of sirolimus. In 3 of the 5 patients, there was a concomitant administration of calcineurin inhibitor. Hypertriglyceridemia (triglycerides ≥600 mg/dL) was noted in 4 (27%) patients, whereas hemolytic uremic syndrome occurred in 1 patient (7%). Two (13%) patients did not have evidence of sirolimus-related toxicity. The correlation between sirolimus blood levels and the occurrence of adverse events has been analyzed in detail. Overall, supratherapeutic (>15 ng/mL) sirolimus levels were noted in 45% of measured values, and very high levels (≥25 ng/mL) were noted in 20% of measured values. All patients who developed nephrotoxicity, 3 of 6 patients who developed neutropenia, and 6 of 9 patients who developed thrombocytopenia had high sirolimus levels (≥25 ng/mL) at the time of the toxic event. Of note, 5 patients developed hematologic toxicity despite normal sirolimus levels (Table 1). For patients with high sirolimus levels, the median oral dose of sirolimus at the time of testing was 2 mg/d (range, 1-4 mg/d). Nine (60%) patients discontinued sirolimus after a median of 43 days (range, 23-139 days) because of nephrotoxicity (n = 4), cytopenia (n = 2), relapse (n = 2), or resolution of cGVHD (n = 1). Two of the 4 patients who discontinued sirolimus because of nephrotoxicity were receiving a concomitant calcineurin inhibitor. Three of the 6 pa-

Table 1. *Drug Levels and Adverse Events Observed in Patients Receiving Sirolimus*

Patient No.	Oral Dose of Sirolimus (mg)*	Time to Start Sirolimus from HSCT (d)	Sirolimus Level (ng/mL)†	Toxicity	Laboratory Value	Concomitant IST	Outcome
100A	2	5760	25	Nephrotoxicity	Creatinine (mg/dL): 2.7	CSA	Normalized, no sirolimus dose modification
1519	2	10	29	Nephrotoxicity	Creatinine (mg/dL): 4.4	—	Normalized, no sirolimus dose modification
241	2	27	32	Nephrotoxicity	Creatinine (mg/dL): 2.0	—	Normalized after withdrawal of sirolimus
220	3	220	25	Nephrotoxicity	Creatinine (mg/dL): 2.0	Tacrolimus	Normalized after dose reduction of sirolimus
218	2	26	26	Nephrotoxicity	Creatinine (mg/dL): 2.6	CSA	Normalized after dose reduction of sirolimus
233	4	284	42	Neutropenia	ANC/μL: 500	MMF	Normalized after G-CSF
1520	2	31	40	Neutropenia	ANC/μL: 250	—	Persistent poor marrow function after G-CSF administration
241	2	27	50	Neutropenia	ANC/μL: 925	—	Normalized without G-CSF
243	4	99	NR	Neutropenia	ANC/μL: 580	—	Normalized after G-CSF
1051	4	37	NR	Neutropenia	ANC/μL: 590	MMF	Normalized without G-CSF
1044	8	49	NR	Neutropenia	ANC/μL: 550	MMF	Normalized after G-CSF
243	4	99	NR	Thrombocytopenia	Platelets/μL: 18 000	Tacrolimus	Normalized after withdrawal of sirolimus
220	3	220	25	Thrombocytopenia	Platelets/μL: 41 000	Tacrolimus	Persistent thrombocytopenia
218	2	26	20	Thrombocytopenia	Platelets/μL: 27 000	CSA	Normalized after dose reduction of sirolimus
233	4	284	42	Thrombocytopenia	Platelets/μL: 50 000	MMF	Normalized after withdrawal of sirolimus
250	3	14	50	Thrombocytopenia	Platelets/μL: 50 000	MMF	Normalized after withdrawal of sirolimus
232	1	86	31	Thrombocytopenia	Platelets/μL: 29 000	—	Normalized after withdrawal of sirolimus
1520	2	31	40	Thrombocytopenia	Platelets/μL: 16 000	—	Increase after withdrawal of sirolimus
1519	2	10	NR	Thrombocytopenia	Platelets/μL: 29 000	—	Persistent thrombocytopenia
241	2	27	50	Thrombocytopenia	Platelets/μL: 14 000	—	Normalized after withdrawal of sirolimus

HSCT indicates hematopoietic stem cell transplantation; IST, immunosuppressive treatment; NR, normal range; ANC, absolute neutrophil count; CSA, cyclosporine; MMF, mycophenolate mofetil; G-CSF, granulocyte colony-stimulating factor.

*Dose of sirolimus administered at the time of corresponding trough level measurement.

†The levels are expressed as the maximum sirolimus measurement during the 7-day period preceding the toxic event.

tients who received sirolimus as treatment of cGVHD showed objective responses (2 complete responses and 1 partial response), and 5 of the 9 patients who received sirolimus as GVHD prophylaxis developed either acute or chronic GVHD; however, given the small sample size and the retrospective nature of the study, these findings should be interpreted with caution.

The incidence of renal toxicity and hemolytic uremic syndrome observed in our series was comparable to that reported by Johnston et al. [1] (40% versus 50%, respectively). This observation confirms that the rate of sirolimus-related nephrotoxicity after allogeneic HSCT is much higher than the rate reported in the renal transplant patient population [2]. However, it should be underscored that 13 of 15 patients included in our study received sirolimus because of nephrotoxicity due to prior exposure to a calcineurin inhibitor, and this fact might have promoted the nephrotoxic effects of sirolimus. Surprisingly, in our experience, the rates of both neutropenia and thrombocytopenia were significantly high: overall, 11 patients (73%) developed cytopenias (5 with thrombocytopenia, 2 with neutropenia, and 4 with thrombocytopenia and neutropenia). Even if we exclude from the analysis patients without a clear correlation between sirolimus administration and cytopenias (ie, patients with autoimmune thrombocytopenia and patients who did not respond to sirolimus dose modification or withdrawal), 33% (5/15) of the patients included in our study developed hematologic toxicity. In this respect, the concomitant therapy with MMF in 4 patients and the pharmacokinetic interaction between the 2 drugs [3] may explain, at least partially, the exaggerated myelosuppressive side effects. High rates of toxic levels of sirolimus have been observed in our study. Many factors, including hepatic dysfunction, intestinal diseases, and the administration of sirolimus, along with other drugs (fluconazole or itraconazole), may be relevant. Of concern was the lack of correlation between sirolimus doses and trough levels, although this finding has been reported previously by others.[4] It should also be emphasized that 36% of the patients who experienced hematologic toxicity had normal sirolimus trough concentrations.

In conclusion, our results strengthen the observations of Johnston and associates and suggest that clinicians must remain vigilant to the potential toxic complications of sirolimus in the stem cell transplant setting. Additional studies to investigate pharmacologic interactions and dose optimization seem warranted.

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