Sirolimus and Thrombotic Microangiopathy after Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

Thrombotic microangiopathy (TMA) may occur after allogeneic hematopoietic stem cell transplantation (HSCT) and is related in part to calcineurin inhibitor toxicity. We observed a higher-than-expected rate of TMA when calcineurin inhibitors were combined with sirolimus. To determine the incidence of and risk factors for TMA after HSCT, we performed a retrospective cohort analysis of myeloablative allogeneic HSCT recipients between 1997 and 2003. TMA diagnosis required the simultaneous occurrence of (1) creatinine increase >2 mg/dL or >50% above baseline, (2) schistocytosis, (3) increased lactate dehydrogenase, and (4) no evidence of disseminated intravascular coagulopathy. A total of 111 sirolimus-exposed subjects were compared with 216 nonexposed subjects after HSCT. TMA occurred in 10.8% of the sirolimus group and 4.2% in the nonsirolimus group (odds ratio, 2.79; $P = .03$). Sirolimus exposure was associated with TMA earlier than in nonsirolimus patients (25 versus 58 days; $P = .04$). Only the use of sirolimus (exact odds ratio, 3.49; $P = .02$) and grade II to IV acute graft-versus-host disease (exact odds ratio, 6.60; $P = .0002$) were associated with TMA in regression analyses. Treatment of TMA varied among affected individuals. Renal recovery was complete in 92% of sirolimus-treated patients. Overall survival after TMA diagnosis was better for sirolimus subjects than for nonsirolimus subjects (58.3% versus 11.1%; $P = .02$). Sirolimus seems to potentiate the effects of calcineurin inhibitors on TMA after HSCT. TMA associated with sirolimus seems reversible and has a favorable prognosis when compared with TMA associated with calcineurin inhibitors alone. A careful monitoring strategy for TMA should be used with a sirolimus-containing graft-versus-host disease prophylaxis regimen.
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INTRODUCTION

Despite significant advances in allogeneic hematopoietic stem cell transplantation (HSCT), graft-versus-host disease (GVHD) and transplant-related toxicity remain as 2 important hurdles to improved outcomes. GVHD prophylaxis with the combination of methotrexate and a calcineurin inhibitor has remained the most commonly used regimen for almost

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2 decades [1]. Methotrexate is associated with significant transplant-related toxicity, including mucositis [2], pulmonary toxicity [3], and delayed engraftment [4,5]. The calcineurin inhibitors have been associated with neurologic toxicity, renal dysfunction, and thrombotic microangiopathy (TMA) after transplantation [6-8]. TMA is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal dysfunction, although the exact definition varies in different published studies of the syndrome [9-13]. The association of TMA with cyclosporine and tacrolimus

after stem cell and solid-organ transplantation is well established [9-12,14,15].

Numerous attempts have been made to develop an effective GVHD prophylaxis regimen associated with less transplant-related toxicity [16-19]. A novel macrocyclic lactone, sirolimus, has been found to have potent immunosuppressive effects in solid-organ transplantation [20-23] and has been studied in stem cell transplantation [24,25]. The use of sirolimus and calcineurin inhibitors in solid-organ and stem cell transplantation has been associated with TMA, [26-31] and there is 1 case report of TMA related to sirolimus monotherapy in a renal transplant patient [26].

In 2 clinical trials of sirolimus in allogeneic stem cell transplantation, GVHD control was noted to be superior to historical controls; however, TMA was noted to occur with increased frequency [24,25]. Because of this apparent increase in TMA incidence, we performed a retrospective cohort study of patients who underwent allogeneic stem cell transplantation between 1997 and 2003 at the Dana Farber Cancer Institute to determine the incidence of and risk factors for TMA.

MATERIALS AND METHODS

Study Design

This was a retrospective single-center cohort analysis of patients who underwent allogeneic HSCT between 1997 and 2003. Patients were included in the study cohort if they received sirolimus as a component of their GVHD prophylaxis regimen during the first 100 days after transplantation and were included in the control cohort if sirolimus was not used. All patients received either a cyclosporine-based or a tacrolimus-based immunosuppressive regimen. Patients who had undergone prior HSCT, who had T-cell depletion as GVHD prophylaxis, whose baseline creatinine was >1.5 mg/dL, or who had a diagnosis of severe veno-occlusive disease (VOD) of the liver were excluded from this analysis. Subjects for the case and control populations were accrued concurrently, although sirolimus-exposed subjects were accrued from 2000 onward only. Case and control cohort subjects were identified by review of electronic medical records.

TMA Definition

TMA was defined as the simultaneous occurrence of (1) creatinine increase >2.0 mg/dL or >50% above baseline, (2) schistocytosis (≥2 schistocytes per high-power field), (3) increased lactate dehydrogenase, and (4) no clinical evidence of disseminated intravascular coagulopathy.

Statistical Analysis

A 2-sided Fisher exact test was used to compare the baseline characteristics, acute GVHD, and the incidence of TMA between the 2 treatment cohorts. A logistic regression model was used to estimate the association of treatment groups and TMA incidence, adjusting for other factors. Overall survival was calculated by using the Kaplan-Meier method, and a 2-sided log-rank test was used to test the difference between survival curves.

Demographic (age and sex) and hematologic (underlying disease and remission status at time of transplantation) disease variables were recorded for each patient. Transplantation characteristics recorded included the conditioning regimen, donor characteristics (age, sex, HLA matched versus mismatched, and related versus unrelated), graft type (bone marrow versus peripheral blood stem cells), and GVHD prophylaxis regimen used. Multiple laboratory values were also recorded for all patients, including creatinine, unfractionated lactate dehydrogenase, coagulation parameters, and the presence of schistocytes on peripheral blood smear. Outcome parameters recorded included the occurrence of GVHD, VOD, and diffuse alveolar hemorrhage. Information gathered for all patients with TMA included the time from transplantation to the onset of TMA; peak creatinine; levels of tacrolimus, cyclosporine, and sirolimus at the onset of TMA; neurologic and cardiac signs at the time of diagnosis; treatment administered for TMA; development of chronic renal insufficiency; and the need for chronic hemodialysis. Finally, overall survival was recorded for all patients in this analysis.

RESULTS

A total of 111 and 216 subjects were included in the sirolimus and nonsirolimus groups, respectively. The baseline characteristics of the subjects are summarized in Table 1. The 2 groups of subjects were balanced for demographic parameters; however, more subjects in the sirolimus group received peripheral blood stem cells (50.5% versus 18.1%; $P < .01$) and had unrelated donors (58.6% versus 42.6%; $P < .01$).

During the 6-year period of this retrospective analysis, 21 subjects were identified as having TMA within the first 100 days after allogeneic HSCT. Twelve subjects (10.8%) in the sirolimus group developed TMA, in comparison with 9 subjects (4.2%) in the nonsirolimus group (odds ratio [OR], 2.79; 95% confidence interval [CI], 1.14-6.84; $P = .03$). Not all cases of TMA were recognized clinically at the time of onset.

Onset and Symptoms of TMA

The median time to develop TMA in the sirolimus cohort was 25 days from the time of HSCT, in comparison with 58 days for the control group ($P = .01$; Table 2). In addition to the requisite symptoms and