Hepatic veno-occlusive disease after tranexamic acid administration in patients undergoing allogeneic hematopoietic stem cell transplantation

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Tranexamic acid is one of the widely used antifibrinolytic agents. In spite of its effective inhibitory activity against plasminogen, thromboembolic adverse events caused by tranexamic acid are rare. We encountered three recipients of allogeneic hematopoietic stem cell transplantation (HSCT) who developed hepatic veno-occlusive disease (VOD) shortly after the administration of tranexamic acid. Hepatic VOD was resolved completely in all patients with the discontinuation of the drug, and with supportive measures with or without intravenous tissue plasminogen activator administration. These findings suggest that administration of tranexamic acid could be one of the possible risk factors for developing hepatic VOD in HSCT recipients. Am. J. Hematol. 82:838–839, 2007. © 2007 Wiley-Liss, Inc.

Introduction

Hepatic veno-occlusive disease (VOD) is one of the life-threatening complications that can occur after hematopoietic stem cell transplantation (HSCT). It is characterized by a syndrome of jaundice, fluid retention, weight gain, and painful hepatomegaly [1,2]. Previous studies identified independent risk factors for developing hepatic VOD after HSCT, including pretransplant liver dysfunction, previous HSCT, and intensive conditioning regimens. It has also been reported that several drugs are associated with the development of hepatic VOD, including busulfan (especially in combination with melphalan), methotrexate, and gemtuzumab ozogamicin [1–7]. We here report three cases of hepatic VOD in which hepatic VOD developed shortly after the administration of tranexamic acid used for bleeding episodes occurring shortly after allogeneic HSCT.

Case Report

Patient 1

A 59-year-old woman with acute lymphoblastic leukemia underwent cord blood transplantation from a human leukocyte antigen (HLA)-mismatched unrelated donor. The conditioning regimen consisted of total body irradiation (TBI; 12 Gy), cytarabine (4 g/m^2), and cyclophosphamide (120 mg/kg). All of the results of the laboratory tests of liver function were within the normal range just prior to conditioning. Tacrolimus and short-term methotrexate were used as a prophylaxis for graft-versus-host disease (GVHD). On day 28, the patient accidentally developed painful intramuscular hematoma in the left thigh, which was confirmed by computed tomography. Three doses of tranexamic acid 1,000 mg were intravenously given on days 28, 29, and 30, in addition to immediate platelet transfusion. On day 32, the serum bilirubin level started rising together with painful hepatomegaly and fluid retention, and the patient became thrombocytopenic, which was refractory to platelet transfusion. The clinical diagnosis of hepatic VOD was made. The patient was treated with intravenous administration of recombinant tissue plasminogen activator (0.25 mg/kg on the first day, followed by 0.5 mg/kg for 3 days), plasma exchange, and hemodialysis for renal impairment. With these treatments, liver and renal function completely resolved.

Patient 2

A 12-year-old boy was diagnosed as having myelodysplastic syndrome, secondarily developing 10 months after his first high-dose chemotherapy (busulfan, etoposide, and melphalan) and autologous peripheral blood stem cell transplantation for acute promyelocytic leukemia. The patient underwent bone marrow transplantation (BMT) from an HLA-matched unrelated donor after being conditioned with TBI (12 Gy), cytarabine (8 g/m^2), and cyclophosphamide (120 mg/kg). All of the results of the laboratory tests of liver function were within the normal range just prior to conditioning. Tacrolimus and short-term methotrexate were used as a prophylaxis against GVHD. On day 5, the patient developed massive hematuria of unknown etiology, requiring red cell transfusion. In addition to red cell and platelet transfusion, three doses of tranexamic acid (500 mg) were given intravenously on days 5 and 6. On day 7, the serum bilirubin level started rising together with painful hepatomegaly, fluid retention, and progressive thrombocytopenia, and the diagnosis of hepatic VOD was made. The patient was treated with intravenous administration of recombinant tissue plasminogen activator (0.25 mg/kg for 4 days) and fluid management. Hepatic VOD was completely improved with these treatments.

Patient 3

A 53-year-old woman with myelofibrosis underwent allogeneic BMT from an HLA serologically matched unrelated

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TABLE I. Clinical Course and Parameters of Three Patients with Hepatic VOD

	Age (years)	Onset of hepatic VOD (post-transplant days)	Maximum bilirubin (mg/dL)	Weight gain (%)	Platelet count (10^9/L)
Patient 1	59	32	57.1	14.5	6.0
Patient 2	12	7	1.2[a]	13.1	6.0
Patient 3	53	11	2.3	9.1	<5.0

VOD, veno-occlusive disease.
[a]Serum bilirubin level was 0.1 mg/dL before the onset of hepatic VOD.

donor. The conditioning regimen consisted of TBI (8 Gy), fludarabine (125 g/m^2), and melphalan (140 mg/m^2). All the results of laboratory tests of liver function were within the normal range just prior to conditioning. Tacrolimus and short-term methotrexate were used as a prophylaxis against GVHD. On day 9, the patient developed hemorrhagic cystitis with progressive anemia requiring red cell and platelet transfusion. Six doses of tranexamic acid (250 mg) were given intravenously on days 10, 11, and 12. On day 11, the serum bilirubin level started rising together with painful hepatomegaly, fluid retention, and progressive thrombocytopenia, and the diagnosis of hepatic VOD was made. The patient was treated supportively with fluid management, which yielded gradual improvement of liver function.

Discussion

Tranexamic acid is an antifibrinolytic agent that binds to plasminogen and blocks the binding of plasminogen to fibrin and its transformation to its activated form. Tranexamic acid has been recognized as an effective hemostatic agent for the treatment or prophylaxis of bleeding in a variety of settings [8–11]. In this report, we presented three recipients of HSCT who developed hepatic VOD shortly, within 1–4 days, after initiating tranexamic acid administration (Table I). The incidence of hepatic VOD after allogeneic HSCT has varied in the literature. In particular, Patient 2 in our report was at high risk for developing hepatic VOD because of the prior high-dose chemotherapy and HSCT. Therefore, the development of hepatic VOD in our cases might be coincidental. However, a notably short duration between the tranexamic acid administration and the onset of hepatic VOD suggested a causative relationship. In spite of its prominent inhibitory activity against fibrinolysis, a causative relationship between tranexamic acid and thromboembolism has not been shown, except in a few reported cases [12–15]. Regarding HSCT recipients, there have been no reports regarding tranexamic acid-associated thromboembolic events, including hepatic VOD. However, recipients of HSCT are considered to be in hypercoagulable states mainly caused by the endothelial damage due to conditioning, calcineurin inhibitors, GVHD, and various infectious complications that could contribute to the development of hepatic VOD and thrombotic microangiopathy. In particular, plasminogen activator inhibitor-1 (PAI-1), a physiological inhibitor of plasminogen activation, is reported to be one of the specific markers of hepatic VOD, suggesting that dysregulated fibrinolysis could play some role in the pathogenesis of VOD [16,17]. The possible role of PAI-1 in the development of hepatic VOD has also been demonstrated in a murine model [18]. These findings suggested that tranexamic acid inhibits plasminogen activation as well could trigger or accelerate the development of hepatic VOD.

In conclusion, transplant physicians should be aware of the possible role of tranexamic acid in the development of hepatic VOD, and should be cautious in using tranexamic acid for the bleeding episode after HSCT.

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