Recombinant Human Tissue Plasminogen Activator for the Treatment of Established Severe Venocclusive Disease of the Liver After Bone Marrow Transplantation

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Seven patients were treated with recombinant human tissue plasminogen activator (tPA) for severe hepatic venocclusive disease (VOD) that developed after bone marrow transplantation for hematologic malignancy. Recombinant human tPA (10 mg/d × 2 days) and heparin (1,000 U bolus followed by continuous intravenous infusion of 150 U/kg/d × 10 days) were begun a median of 9 days (range, 4 to 18 days) posttransplant. The median total serum bilirubin and percent weight gain from baseline were 19.4 mg/dL (range, 14.6 to 34.9 mg/dL) and 9.1% (range, 1% to 18.5%), respectively, at the start of tPA administration. Five patients responded to therapy with prompt reduction in total serum bilirubin within 96 hours of starting tPA. Three patients are alive 178 to 379 days posttransplant without evidence of VOD. No patient had significant hemorrhagic complications with tPA. We conclude that recombinant human tPA can be administered to patients with severe VOD at the dosage described. Whereas preliminary data suggests that recombinant human tPA can alter the natural history of severe VOD, further study is necessary to determine its efficacy.

VENOCCLUSIVE disease (VOD) of the liver, a clinical syndrome characterized by hepatomegaly, fluid retention, and hyperbilirubinemia, is the result of endothelial damage and hepatocyte injury in zone 3 of the liver acinus. In the bone marrow transplant (BMT) setting, VOD is caused by dose-intensive chemotherapy or chemoradiotherapy used to prepare patients for transplant.[1-4] VOD occurs in more than 50% of patients who undergo BMT at our center and is responsible for more than 15% of deaths.[5] Hepatitis before the start of conditioning therapy, certain high-dose regimens, persistent fever in the early preconditioning and postconditioning period, and BMT from mismatched or unrelated donors are independent risk factors for the development of VOD.[5,6] Severe VOD is frequently accompanied by renal failure, pulmonary edema, and encephalopathy.[2,4,5] Ninety-eight percent of patients who develop severe disease die by day 100, and of these, multiorgan failure related to VOD contributes to or causes death in more than 90%.[5]

Histologically, VOD is characterized by deposition of factor VIII and fibrinogen in the subendothelial zones of affected venules and by necrosis of hepatocytes in zone 3 of the liver acinus.[3] Prophylaxis of VOD with heparin has had mixed results.[7-9] Baglin et al[10] reported on a patient with VOD after autologous BMT for multiple myeloma who received 200 mg of recombinant human tissue plasminogen activator (tPA) over 4 days. Improvement in encephalopathy and liver function tests was observed within 48 hours of the start of tPA administration, and the patient was discharged from the hospital 9 days after the start of therapy. There have been two other case reports of the successful treatment of severe VOD using recombinant tPA.[11,12]

We conducted a pilot study of recombinant tPA and heparin to determine its safety and clinical response in patients with severe VOD after BMT. Patients were selected based on a high probability of dying of multiorgan failure as a result of VOD.[13] Patients were excluded if, in the judgement of the investigators, the risk of catastrophic hemorrhage was felt to be excessive. We report here the results of tPA administration in seven consecutive patients.

MATERIALS AND METHODS

Patient selection. Patients with a clinical diagnosis of severe VOD were eligible for entry into this trial. VOD was defined according to McDonald et al[2] as having two of the following before day 30 posttransplant: jaundice, hepatomegaly and/or right upper quadrant pain, ascites and/or unexplained weight gain. Two groups have previously shown that more than 88% of patients with histologic evidence of VOD were diagnosed independently by the clinical criteria above.[4,5] Nonetheless, other causes for liver dysfunction[14-16] cannot be definitively ruled out in these patients. For the purposes of this clinical trial, entry criteria included a clinical diagnosis of VOD with total serum bilirubin of ≥ 15 mg/dL caused by VOD by day 20 posttransplant and one of the following: weight gain of 5% or greater from baseline (weight immediately before the start of preparative therapy); encephalopathy caused by VOD; or renal insufficiency defined as doubling of preconditioning creatinine coincident with the development of VOD and not caused by nephrotoxic antibiotics or cyclosporine. Such patients have a greater than 80% probability of dying of multiorgan failure within 100 days of transplant.[5] Patients were excluded from entry into the study for any of the following reasons: liver dysfunction whose etiology was likely to be caused by diseases other than VOD; gross hemoptysis, melena, hematochezia, or epistaxis; history of any central nervous system lesion; ongoing hemodialysis or mechanical ventilation; uncontrolled hypertension; or preexisting hemostatic disorders excluding disease-related or chemotherapy-related thrombocytopenia. Initially, patients were required to achieve platelet counts of $\geq 30{,}000/mm^3$ after platelet transfusion. This requirement was modified to $\geq 15{,}000/mm^3$ when it became clear that most patients who were otherwise eligible were refractory to platelet transfusion and over time developed renal or pulmonary failure that excluded them from study entry. Also, the first three patients entered did not have any bleeding complications. One

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patient was entered into the study with a total serum bilirubin of 14.6 mg/dL (UPN 4116). Based on her total serum bilirubin and percent weight gain above baseline, her probability of developing severe VOD was estimated to be 71%.[13] Because of the high probability of developing severe and ultimately fatal VOD, and a rapidly increasing serum creatinine, she was offered this treatment protocol while her bilirubin was still less than 15.0 mg/dL. Patients who had an abnormal mental status or signs of central nervous system dysfunction underwent computed tomography scans of the head before the start of therapy to ensure that no occult central nervous system bleeding had occurred. Patients or their next of kin gave written informed consent in accordance with the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Day 0 is the day of marrow infusion.

Drug administration. Recombinant human tPA (Activase) was supplied by Genentech, Inc (South San Francisco, CA). Patients received 10 mg of tPA administered by intravenous infusion over 4 hours on each of 2 consecutive days. Simultaneous with starting tPA, patients received a bolus of 1,000 U heparin intravenously, followed by a continuous heparin infusion at a rate of 150 U/kg/d. This dose of heparin was shown previously to be tolerated without significant bleeding in patients undergoing BMT.[9]

Patient monitoring. Patients were monitored daily for total serum bilirubin, serum creatinine, urine output, abdominal girth, body weight, liver size and tenderness, evidence of bleeding, and complete blood counts. Platelet count, fibrinogen, fibrin split products, prothrombin time, and partial thromboplastin time (PTT) were obtained before the start of therapy and three times daily for 3 days. Thereafter, coagulation studies were performed daily until the completion of the heparin infusion. Heparin dosage was adjusted if the PTT exceeded 1.2 times the upper limit of control.

RESULTS

Patient characteristics. Seven patients received recombinant human tPA plus heparin as therapy for severe hepatic VOD between February and November 1991. The onset of VOD (defined as the day on which total serum bilirubin exceeded 2.0 mg/dL) occurred a median of 2 days (range, 1 to 8 days) posttransplant (Table 1) and increased rapidly during the 10 days before tPA administration (Table 2). Recombinant tPA administration was begun a median of 9 days (range, 4 to 18 days) posttransplant. All patients were deeply jaundiced, four patients were encephalopathic, three had ascites, five had hepatomegaly and right upper quadrant pain, and four had renal insufficiency (defined as a doubling of the preconditioning serum creatinine) at the start of tPA administration.

Response to thrombolytic therapy. At the start of thrombolytic therapy, the median total serum bilirubin was 19.4 mg/dL (range, 14.6 to 34.9 mg/dL) and the median weight change was 9.1% in excess of weight before cytoreductive therapy (range, 1.0% to 18.5%) (Table 2). Five of seven patients (UPNs 5932, 5989, 6230, 6300, and 6297) had prompt decreases in serum bilirubin. Within 48 and 96 hours after the start of thrombolytic therapy, the mean decreases in total serum bilirubin were 22.3% (range, 11.8% to 36.0%) and 41.8% (range, 28.2% to 55.2%) of pretreatment values, respectively (Fig 1). In four of these five patients, the decline in serum bilirubin continued during the 10-day period of heparin infusion; the mean decrease for these patients at 10 days was 70.7% (range, 57.4% to 88.0%) of pretreatment values (Fig 1). One patient (UPN 6297) had a 40% decline in serum bilirubin, a reduction in liver size, cessation of liver pain, and a diuresis of 3.6 kg within 96 hours of thrombolytic therapy, but then developed sepsis syndrome caused by *Candida albicans,* followed by an increase in bilirubin and renal failure (Table 2 and Fig 1). Some degree of diuresis and weight loss occurred in four patients who had an apparent decrease in bilirubin in response to therapy, but the amount of diuresis was not as striking as the decrease in bilirubin (Table 2).

After the completion of heparin infusion, three patients (UPNs 5932, 6230, and 6300) had complete resolution of signs and symptoms of VOD and are alive greater than 379, 215, and 174 days posttransplant. UPNs 5932 and 6230 are currently receiving treatment for chronic graft-versus-host disease involving the liver. UPNs 5989 and 6297 died 33 and 40 days posttransplant, respectively, of graft-versus-host disease and sepsis syndrome with multiorgan failure.

Two of seven patients (UPN 6342 and 4116) had no apparent response to thrombolytic therapy, both demonstrating progressive increases in both bilirubin and weight in the days after the start of therapy. UPN 6342 died of multiorgan failure 7 days after initiation of thrombolytic therapy. The course of UPN 4116 was characterized by fever, sepsis syndrome, and multiorgan failure on the fourth day following the start of thrombolytic therapy. There are no clear indications why these two patients failed to respond to thrombolytic therapy other than the fact that

Table 1. Characteristics of Seven Patients Who Received Thrombolytic Therapy for Severe VOD

UPN	Age (yr)	Diagnosis	Preparative Regimen	Transplant Type	HLA-Match	Onset of VOD (day*)	Start of t-PA (day*)
5932	43	CML, chronic phase	Bu + Cy†	Allogeneic	Identical	8	16
5989	30	Multiple myeloma	Bu + Cy	Allogeneic	Identical	2	9
6230	43	CML, 2nd blast crisis	Cy + TBI 13.2 Gy	Allogeneic	3-Antigen mismatch	2	18
6300	53	CML, chronic phase	Bu + Cy	Allogeneic	Identical	1	8
6297	36	ALL, 2nd remission	TBI 15.75 Gy + Cy	Allogeneic	Identical	1	4
6342	57	ALL, 1st relapse	TBI 15.75 Gy + Cy	Allogeneic	Identical	2	9
4116	23	ALL, 3rd relapse	Cy + TBI 13.2 Gy	Allogeneic	Matched, unrelated	1	6

Abbreviations: CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation.

*Where day 0 is the day of marrow infusion.

†Bu, 16 mg/kg; Cy, 120 mg/kg.

Table 2. Time Course of Serum Bilirubin and Patient Weight, 10 Days Before and 10 Days After the Start of Thrombolytic Therapy With tPA and Heparin. Day 0 Values Are Those Obtained on the Morning on Which tPA and Heparin Therapy Was Started. Change in Weight Is Expressed as Percent of Weight Before Cytoreductive Therapy

	Days Before Thrombolytic Therapy						Days After Thrombolytic Therapy				
UPN	−10	−8	−6	−4	−2	0	+2	+4	+6	+8	+10
5932											
Total serum bilirubin (mg/dL)	0.5	3.3	8.1	11.8	20.3	34.9	28.1	21.3	11.5	6.3	4.2
Change in weight (% of baseline)	−1.2	+0.7	+4.5	+4.7	+5.5	+1.0	0	−1.6	0	−1.4	−1.2
5989											
Total serum bilirubin (mg/dL)	0.6	2.8	4.0	9.1	13.3	19.5	17.2	14.0	10.4	9.3	8.3
Change in weight (% of baseline)	0.5	+0.7	+3.2	+5.4	+6.7	+9.1	+12.3	+4.9*	+5.0*	+6.4	+7.2
6230											
Total serum bilirubin (mg/dL)	5.9	11.3	17.5	24.0	17.2	19.4	16.6	8.7	6.7	7.0	5.3
Change in weight (% of baseline)	+4.7	+5.4	+6.2	+8.5	+11.0	+11.4	+11.1	+10.1	+7.8	+6.5	+5.2
6300											
Total serum bilirubin (mg/dL)	1.1	1.2	4.3	4.7	14.6	20.2	14.2	10.7	8.0	6.5	5.5
Change in weight (% of baseline)	+3.2	+7.0	+9.0	+6.3	+5.9	+5.1	+4.3	+5.7	+6.5	+6.8	+5.5
6297											
Total serum bilirubin (mg/dL)	0.7	0.8	0.9	8.9	10.3	16.1	10.3	9.7	16.9	26.9	26.2
Change in weight (% of baseline)	+3.0	−0.7	+2.1	+9.6	+11.7	+5.6	0.4	+4.7	+5.2	+6.2	+6.0
6342											
Total serum bilirubin (mg/dL)	1.8	5.6	7.0	6.0	8.7	19.0	28.0	46.4	46.7	—	—
Change in weight (% of baseline)	+4.9	+7.5	+12	+12.1	+11.6	+14.9	+18	+20.5	+21	—	—
4116											
Total serum bilirubin (mg/dL)	0.5	0.9	3.1	5.9	11.0	14.6	17.0	29.3	29.2	33.0	37.6
Change in weight (% of baseline)	+2.9	+4.3	+7	+13.5	+15.6	+18.5	+18.2	+5.7*	+15.2*	+14.2*	+6.8*

*Patient on hemodialysis.

both had gained more weight before therapy (14.9% and 18.5% of baseline weight, respectively) than the five patients who seemed to respond (mean 6.4% increase; range, 1.0% to 11.4%) (Table 2).

Bleeding. Life-threatening bleeding did not occur in patients entered into this trial. One patient (UPN 4116) had vaginal bleeding and bleeding from a Swan-Ganz catheter site 4 days after the start of tPA, when fibrinogen and PTT were 365 mg/dL and 39.0 seconds, respectively; her heparin infusion was stopped at that time. Three patients had minor bleeding characterized by Hemoccult-positive (SmithKline, San Jose, CA) stools in one patient and bleeding from oral mucositis in two patients. Fibrinogen levels were measured three times a day during tPA administration and daily thereafter until the cessation of heparin. The mean plasma fibrinogen was 427 mg/dL (range, 266 to 796 mg/dL) before the start of tPA administration and 373 mg/dL (range, 208 to 515 mg/dL) 24 hours after the second dose of tPA. The lowest fibrinogen measured was 140 mg/dL 5 days after completion of tPA infusion in UPN 4116, who was septic at the time.

DISCUSSION

This study was designed to determine the safety of recombinant human tPA in patients with severe VOD and to attempt to determine its efficacy in this setting. Entry criteria were written to include those patients with VOD

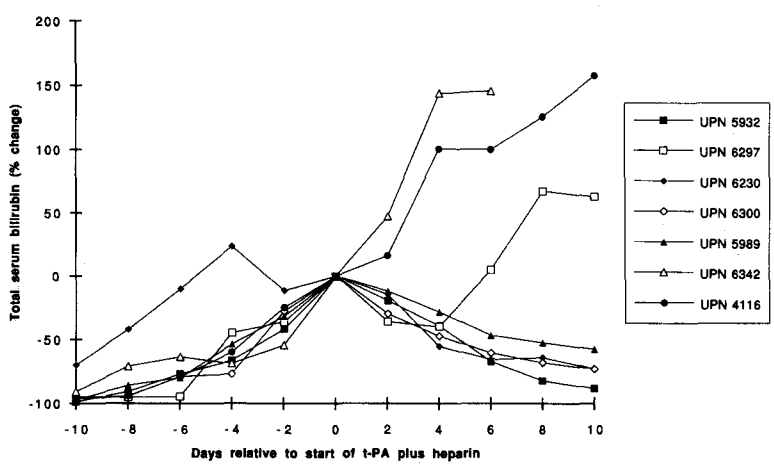

Fig 1. Total serum bilirubin expressed as percent change during the 10-day periods before and after the start of thrombolytic therapy. Day 0 relative to start of tPA plus heparin indicates the day on which therapy with tPA and heparin began.

whose survival at day 100 was predicted to be less than 20%. Five of seven patients treated with tPA showed a prompt reduction in total serum bilirubin within 96 hours of starting medication. Three patients survived and are currently alive 178 to 379 days posttransplant. Two of these patients are under treatment for chronic graft-versus-host disease involving the liver, but all have total serum bilirubins of less than 2.0 mg/dL and all have returned to their baseline weights.

The accrual of patients into this clinical trial was slow, despite the high incidence of VOD at our institution. Patients were excluded who could not achieve platelet counts greater than 15,000/mm^3. Patients with severe VOD are frequently refractory to platelet support,[5,17] which is required to achieve hemostasis during a time when the grafted marrow is not producing platelets. There is little published experience in the use of tPA in patients with profound thrombocytopenia. We also excluded patients who were intubated, were undergoing dialysis, or were actively bleeding because we were reluctant to expose them to the additional risk of fatal bleeding. Thus, we were quite selective regarding patient entry into the study. We do not know whether any of the patients who were excluded for the reasons above might have benefited from tPA. A larger number of marrow transplant patients might achieve benefit if tPA could be administered before intubation, dialysis, or bleeding occurred.

The dosage of tPA used in this trial is small by most standards, but most of the experience with thrombolytic therapy is in patients with normal platelet counts and without liver dysfunction. The TIMI trial[18] treated myocardial infarction patients with either 100 or 150 mg of tPA, heparin (5,000 U bolus followed by 1,000 U/h), and aspirin. In that study, hemorrhagic events were associated with a higher dosage of tPA, prolongation of the PTT to more than 90 seconds, extent of fibrinolysis, and peak tPA levels. Much smaller doses of tPA have been used successfully for the treatment of peripheral arterial and venous thromboses.[19-21] In many reports of tPA administration, heparin has been administered concomitantly[18,21] or after successful thrombolysis.[20,21] Rapold et al reported that, in the dog model, the combination of tPA and heparin was significantly better than tPA alone for arterial and venous thrombolysis.[22] The appropriate dosage of tPA, the optimal time of administration, and the need for supplying other anticoagulants, such as protein C,[23] remain unanswered questions in the setting of VOD after BMT. From our experience in treating patients with severe VOD, we suggest that, if tPA is to be effective, it should be administered earlier rather than later, before the accumulation of large amounts of fluid and the development of multiorgan failure.

In the current study, four patients had evidence of bleeding while on either tPA or heparin. One patient in our study had guaiac-positive stools, two had bleeding from oral mucositis, and one had bleeding from both the vagina and a Swan-Ganz catheter site in the groin. Bleeding is common after BMT, with as many as 90% of patients having minor bleeding.[9] Whereas life-threatening bleeding did not occur in the patients treated in this study, the risk of catastrophic bleeding after tPA administration in the setting of profound thrombocytopenia is high.

Thrombolytic therapy is a rational approach to the treatment of VOD. VOD does not commonly lead to fulminant hepatic failure, but rather leads to multiorgan failure largely through its effects on renal function. Obstruction to sinusoidal blood flow caused by lesions in the terminal hepatic venules leads to an acute hepatorenal syndrome. Factor VIII and fibrinogen within the subendothelial zones of affected terminal hepatic venules seem to be a major component in the obstruction of sinusoidal blood flow.[3] Our experience demonstrating an initial response to tPA infusion in five of seven patients supports the hypothesis that thrombosis is an important event in the pathogenesis of VOD. Although prospective studies at our institution have shown that the probability of patients with severe VOD surviving to day 100 posttransplant is less than 10%,[5] we cannot rule out the possibility that some or all of these patients would have improved without tPA. Only a prospective, randomized trial can determine the efficacy of tPA for severe VOD.

NOTE ADDED IN PROOF

Since submission of this manuscript, an additional three patients received recombinant human tPA for severe VOD. One patient (UPN 6203) received a total of 20 mg of tPA (10 mg on 2 successive days). Two patients (UPNs 6535 and 6609) received a total of 40 mg of tPA (10 mg on 4 successive days). UPN 6203 developed hematemesis 7 days after the last dose of tPA, while receiving heparin. Bleeding was controlled with discontinuation of heparin. This patient did respond to treatment with tPA and heparin. UPN 6535 had a 58% reduction in total serum bilirubin 10 days after initiating therapy, and UPN 6609 had a 44% reduction in total serum bilirubin at 10 days. As of August 27, 1992, 5 of 10 patients who received recombinant human tPA and heparin for severe VOD are alive and well 170, 223, 363, 404, and 568 days posttransplant.

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