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 x 2 days) and heparin (1,000 U bolus followed by continuous intravenous infusion of 150 U/kg/d x 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.

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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 greater than 80% probability of dying of multiorgan failure within 100 days of transplant. 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 nephrotoxic antibiotics or cyclosporine. Such patients have a greater than 80% probability of dying of multiorgan failure within 100 days of transplant. 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 nephrotoxic antibiotics or cyclosporine. Such patients have a greater than 80% probability of dying of multiorgan failure within 100 days of transplant. 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 nephrotoxic antibiotics or cyclosporine. Such patients have a greater than 80% probability of dying of multiorgan failure within 100 days of transplant.
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%. 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 on a median of 2 days (range, 1 to 8 days) after transplantation (Table 1 and Fig 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) after transplantation. 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). 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 VOD (defined as the day on which total serum bilirubin and percent weight gain above baseline were both less than 15.0 mg/dL) and had complete resolution of bilirubin in response to therapy, and in these patients the amount of diuresis was not as striking as the decrease in bilirubin (Table 2).

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

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Preparative Regimen</th>
<th>Transplant Type</th>
<th>HLA Match</th>
<th>Onset of VOD (day*)</th>
<th>Start of t-PA (day*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5932</td>
<td>43</td>
<td>CML, chronic phase</td>
<td>Bu + Cy</td>
<td>Allogeneic</td>
<td>Identical</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>6230</td>
<td>43</td>
<td>CML, 2nd blast crisis</td>
<td>Cy + TBI 13.2 Gy</td>
<td>Allogeneic</td>
<td>Identical</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>6300</td>
<td>53</td>
<td>CML, chronic phase</td>
<td>Bu + Cy</td>
<td>Allogeneic</td>
<td>Identical</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>6297</td>
<td>36</td>
<td>ALL, 2nd remission</td>
<td>TBI 15.75 Gy + Cy</td>
<td>Allogeneic</td>
<td>Identical</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>6342</td>
<td>57</td>
<td>ALL, 1st relapse</td>
<td>TBI 15.75 Gy + Cy</td>
<td>Allogeneic</td>
<td>Identical</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>4116</td>
<td>23</td>
<td>ALL, 3rd relapse</td>
<td>Cy + TBI 13.2 Gy</td>
<td>Allogeneic</td>
<td>Matched, unrelated</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

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.
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 Hemocult-positive (SmithKline, San Jose, CA) stool 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

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**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.**

<table>
<thead>
<tr>
<th>UPN</th>
<th>Days Before Thrombolytic Therapy</th>
<th>Days After Thrombolytic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-10</td>
<td>-8</td>
</tr>
<tr>
<td>5932</td>
<td>Total serum bilirubin (mg/dL)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Change in weight (% of baseline)</td>
<td>-1.2</td>
</tr>
<tr>
<td>5969</td>
<td>Total serum bilirubin (mg/dL)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Change in weight (% of baseline)</td>
<td>0.5</td>
</tr>
<tr>
<td>6230</td>
<td>Total serum bilirubin (mg/dL)</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Change in weight (% of baseline)</td>
<td>+4.7</td>
</tr>
<tr>
<td>6300</td>
<td>Total serum bilirubin (mg/dL)</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Change in weight (% of baseline)</td>
<td>+3.2</td>
</tr>
<tr>
<td>6297</td>
<td>Total serum bilirubin (mg/dL)</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Change in weight (% of baseline)</td>
<td>+3.0</td>
</tr>
<tr>
<td>6342</td>
<td>Total serum bilirubin (mg/dL)</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Change in weight (% of baseline)</td>
<td>+4.9</td>
</tr>
<tr>
<td>4116</td>
<td>Total serum bilirubin (mg/dL)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Change in weight (% of baseline)</td>
<td>+2.9</td>
</tr>
</tbody>
</table>

*Patient on hemodialysis.

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/mm³. Patients with severe VOD are frequently refractory to platelet support, 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 much of the experience with thrombolytic therapy is in patients with normal platelet counts and without liver dysfunction. The TIMI trial²⁶ 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 PT 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 concomitantly²⁸,²¹ or after successful thrombolysis.²² 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.²³ The appropriate dosage of tPA, the optimal time of administration, and the need for supplying other anticoagulants, such as protein C,²¹ 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.³ 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%,³ 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.

REFERENCES

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SI Bearman, MC Shuhart, MS Hinds and GB McDonald