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Veno-Occlusive Disease(VOD) of the Liver in Korean Patients following Allogeneic Bone Marrow Transplantation(BMT) : Efficacy of Recombinant Human Tissue Plasminogen Activator (rt-PA) Treatment

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Veno-occlusive disease (VOD) of the liver is a clinical syndrome characterized by hyperbilirubinemia, painful hepatomegaly, and fluid retention. In the bone marrow transplantation (BMT) setting, VOD is caused by dose-intensive chemotherapy and / or radiotherapy used to prepare patients for transplant. VOD occurs in up to 50 % of the patients who undergo BMT and is usually associated with a high mortality rate. Until recently, there was no proven effective medical therapy for this condition once it was clinically apparent. We report here on the frequency and treatment result of VOD with rt-PA in our allogeneic BMT patients. Eight patients (median age 28.5 years) underwent allogeneic BMT from December, 1993 to June, 1995 in Asan Medical Center. Six leukemia patients were prepared for BMT with busulfan and cyclophosphmide, while two aplastic anemia patients received cyclophosphamide and antithymocyte globulin. VOD was defined as having two of the following features before day 20 posttransplant : jaundice (bilirubin $\geq$ 2 mg / dL), tender hepatomegaly and / or right upper quadrant pain, ascites and / or unexplained weight gain(>2 % from baseline). All patients who were diagnosed with VOD received rt-PA (10-20 mg / day) and heparin(10,000 U / day). Three(37.5 %) of the eight patients developed VOD that occurred between 6 and 10 days posttransplant. All three patients developed jaundice, weight gain, and tender hepatomegaly. Ascites and renal insufficiency occurred in two patients and pleural effusion in one patient. rt-PA and heparin were begun 6 to 26 days posttransplant and rt-PA was administered for 7 to 14 days. All three patients responded to the therapy ; bilirubin levels began to decrease at 4 to 13 days from the start of therapy. They are all alive at day 111, 316, and 548 days posttransplant. None of the patients had significant hemorrhagic complications after rt-PA treatment. Prolonged administration of rt-PA was feasible without bleeding episode and it seems that rt-PA may alter the natural course of VOD.

Key Words : *rt-PA, VOD, BMT*

INTRODUCTION

The clinical syndrome of veno-occlusive disease (VOD) of the liver is one of several manifestations of regimen-related toxicities that can occur after high-dose cytoreductive therapy (Bearman et al., 1988). Clinically, VOD of the liver is characterized by hyperbilirubinemia, painful hepatomegaly, and fluid retention. In the bone marrow transplantation (BMT) setting, VOD is caused by dose-intensive chemotherapy and/or radiotherapy used to prepare patients for transplant, and is a major cause of early morbidity and mortality (McDonald et al., 1993). Incidence of up to 50 % was reported and cases classified as severe VOD are associated with a high mortality rate (Bearman, 1995). Endothelial damage, due to the conditioning regimen, is believed to be the key event in the pathogenesis of VOD. This endothelial injury triggers the coagulation cascade, induces the deposition of coagulation factors and fibrin in the adventitial and subendothelial zones of the hepatic venules, and eventually leads to fibrous obliteration of the affected venules. 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 (Shulman et al., 1987). Until recently, there was no effective medical therapy for this condition, once it was clinically apparent. There are, however, several reports on the successful treatment of VOD using recombinant tissue plasminogen activator (rt-PA) (Baglin, 1994). We report here on the frequency of VOD and results of treatment with rt-PA in our allogeneic bone marrow transplant patients.

MATERIALS AND METHODS

The material consisted of eight patients who underwent allogeneic bone marrow transplantation from December, 1993 to June, 1995 in Asan Medical Center. The median age of patients was 28.5 years (range, 18-42). There were six males and two females. Six patients underwent BMT for treatment of leukemia : two of them had chronic myelogenous leukemia (CML) in chronic phase, one CML in accelerated phase, one acute lymphoblastic leukemia (ALL) in first remission, one ALL in first relapse, and one acute myelogenous leukemia (AML) in first remission. The other two patients received transplants for the treatment of severe aplastic anemia (AA).

Preparative regimens were 'busulfan (16 mg/kg) *plus* cyclophosphamide (120 mg/kg)' for the patients with leukemia, and 'cyclophosphamide (200 mg/kg) *plus* antithymocyte globulin (ATG, 90 mg/kg)' for aplastic anemia. Bone marrow donors were HLA matched siblings in all cases.

All patients were evaluated for hepatitis B and C, cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein-Barr virus (EBV). All patients had pre-transplant coagulation screening that consisted of prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen. Measurements of serum creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase were done before BMT and at least twice weekly.

All patients were nursed in laminar air flow rooms. Ciprofloxacin and acyclovir were administered for gut decontamination and viral prophylaxis, respectively. Hyperhydration and mesna were given for the prevention of cyclophosphamide-induced hemorrhagic cystitis. All blood products were leukocyte-depleted by filtration and irradiated. Intravenous immunoglobulin 500 mg/kg was administered at day-7, then once every other week for twelve times. All patients received prophylactic therapy for graft-versus-host disease (GVHD) with cyclosporine and methotrexate. Cyclosporine was given 1.5 mg/kg intravenously every 12 hours starting on day-1, then was converted to two 6.0 mg/kg doses given orally at discharge and was tapered from day 60 to day 240. Intravenous methotrexate were given at the dose of 15 mg/m^2 on day 1 and 10 mg/m^2 on day 3, 6, and 11. On day 0, the marrow from the donor was infused over 3-4 hours. If there was minor ABO mismatch between donor and recipient, the marrow was infused after the removal of plasma. Recombinant human granulocyte colony stimulating factor (rhG-CSF) 300 or 450 μg was given intravenously once daily starting at day 0 or 5. Total parenteral nutrition was given when needed.

A diagnosis of VOD was made according to a clinical criteria as having two of the following before

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day 20 posttransplant : (1) hyperbilirubinemia (bilirubin ≥ 2 mg/dL), (2) hepatomegaly or right upper quadrant pain of liver origin, and (3) ascites and/or unexplained weight gain (> 2 % from baseline) because of fluid accumulation. No other explanation for these signs and symptoms could be present at the time of diagnosis (McDonald et al., 1993).

All patients with a clinical diagnosis of VOD received rt-PA (Actylase®) and heparin. Patients received 10 mg of rt-PA administered by intravenous infusion over 4 hours daily. Simultaneously with starting rt-PA, patients received a bolus of 1,000 U heparin intravenously, followed by a continuous heparin infusion at a rate of 10,000 U/day. Administration of rt-PA was continued until bilirubin level and/or weight gain was decreased unless there was bleeding complication. During the treatment of rt-PA and heparin, patients were monitored daily for serum total bilirubin, creatinine, AST, ALT, complete blood counts, urine output, body weight, liver size and tenderness, and evidence of bleeding. Heparin dosage was adjusted if the PTT exceeded 1.2 times the upper limit of control.

RESULTS

Table 1 shows the charateristics of eight bone marrow recipients included in this study. Three (UPN 1, 2, and 3) of eight patients (37.5 %) were diagnosed as having VOD and received rt-PA plus heparin. All three patients were males, and their ages were 22, 41, and 34. The pretransplant disease status was first chronic phase of CML in two patients and first relapse of ALL in one. All three patients received treatment for prophylaxis of VOD. UPN 1 and 2 received pentoxifylline 400 mg orally five times a day. UPN 3 received ursodeoxycholic acid 200 mg orally twice a day in addition to pentoxifylline. On pretransplant examination, UPN 1 and 2 had hepatosplenomegaly. UPN 1 and 2 were hepatitis B virus carrier with normal liver function, and UPN 3 experienced drug-induced hepatitis during pretransplant anti-leukemic chemotherapy with mild transaminase elevation at the time of transplantation. Serologic test for hepatitis C virus was negative in all three patients. IgG antibody for CMV was positive in all three patients. Coagulation profiles were normal in all. In one patients (UPN 1), there were minor ABO mismatch between recipient and donor.

Table 1. Characteristics of the bone marrow recipients

UPN	1	2	3	4	5	6	7	8
Sex	male	male	male	male	female	male	female	male
Age	22	41	34	28	24	18	42	29
Diagnosis	CML	CML	ALL	AA	AML	ALL	CML	AA
Disease status	chronic phase	chronic phase	first relapse	severe	first CR	first CR	accelerated phase	severe
VOD prophylaxis	pentoxiphylline	pentoxiphylline	pentoxiphylline UDCA	UDCA	heparin UDCA	heparin	heparin	heparin
Pretransplant liver disease	HBV carrier	HBV carrier	drug-induce hepatitis	No	HBV carrier	No	No	No
Pretransplant examination								
Hepatomegaly	+(2cm)#	+(1cm)#	–	–	–	–	–	–
Splenomegaly	+(13cm)#	+(2cm)#	–	–	–	–	–	–
AST/ALT	19/13	18/19	32/65	28/45	14/20	17/16	16/11	20/29
HBsAg	+	+	–	–	+	–	–	–
HBsAb	–	–	–	+	–	–	+	+
HCV Ab	–	–	–	–	–	–	–	–
CMV Ab(IgG)	+	+	+	+	+	+	+	+
BM cell dose($\times 10^8$/kg)$	3.77	3.30	6.30	2.54	4.25	3.10	5.23	4.55
ABO(donor→recipient)	$O^+ \rightarrow B^+$	$O^+ \rightarrow O^+$	$A^+ \rightarrow A^+$	$O^+ \rightarrow A^+$	$O^+ \rightarrow O^+$	$O^+ \rightarrow O^+$	$B^+ \rightarrow B^+$	$O^+ \rightarrow AB^+$

* abbreviations : UPN=unit patient number, VOD=veno-occlusive disease, CML=chronic myelogenous leukemia, ALL=acute lymphoblastic leukemia, AA=aplastic anemia, CR=complete remission, UDCA=ursodeoxycholic acid, HBV=hepatitis B virus, AST=aspartate aminotransterase, ALT=alanine aminotransferase, HBsAg=hepatitis B virus antigen, HBsAb=antibody to hepatitis B virus, HCV Ab=antibody to hepatitis C virus, CMV Ab=antibody to cytomegalovirus, BM=bone marrow

length from costal margin.

$ infused total nucleated cells divided by recipient body weight (kg).

The onset of VOD (defined as the day on which serum total bilirubin exceeded 2.0 mg/dL or body weight increase more than 2 % above baseline) occurred between 6 and 10 days posttransplant (Table 2). All three patients developed jaundice, weight gain, and tender hepatomegaly. Maximal level of serum total bilirubin was 6.6, 5.4, and 8.7 mg/dL, and weight gain above baseline was 21 %, 6 %, and 16 %, respectively in UPN 1, 2, and 3. The onset of weight gain preceded the increase of serum bilirubin in all cases. Liver function tests showed mild elevation of serum transaminase in all three patients, and elevation of serum alkaline phosphatase in one (UPN 3). Ascites and renal insufficiency occurred in two patients (UPN 1 and 3), and pleural effusion in one patient (UPN 3). There was no pulmonary infiltrate or cardiac failure.

rt-PA plus heparin was begun 6 to 26 days posttransplant, and administered for 7 to 14 days (Table 3). All three patients improved with the therapy.

Table 2. Clinical manifestations of the patients with VOD

UPN	1	2	3
Jaundice			
maximal bilirubin level	6.6 mg%	5.4 mg%	8.7mg%
onset day/resolved day	11/59	9/28	26/not resolved
Weight gain			
maximal gain(%)#	21 %	6 %	16 %
onset day/resolved day	8/47	6/32	10/79
Tender hepatomegaly			
onset day/resolved day	12/41	4/27	16/69
Ascites			
onset day/resolved day	12/54	–	19/89
Liver function test			
maximal AST level	374	104	335
maximal ALT level	245	233	191
maximal ALP level	229	257	573
Renal insufficiency	Yes	No	Yes
maximal creatinine level	3.0	–	1.7
onset day/resolved day	16/42	–	29/37
Pleural effusion	No	No	Yes(day 20)
Pulmonary infiltrate	No	No	No
Cardiac failure	No	No	No

*abbreviations : UPN=unit patient number, VOD=veno-occlusive disease, AST=aspartate aminotransferase, ALT=alanine aminotransferase, ALP=alkaline phosphatase

#percent increase of body weight from baseline weight.

Table 3. Treatment including thrombolytic therapy for VOD

UPN	1	2	3
rt-PA			
start	day 20	day 6	day 26
dose	10 mg/day	10 mg/day	10→20 mg/day
duration	7 days	14 days	11 days
Heparin			
start	day 20	day 6	day 26
dose	10,000 U/day	10,000 U/day	10,000 U/day
duration	10 days	18 days	12 days
Furosemide administration	Yes	No	Yes
Ascites tap	7 times	No	4 times
Bleeding complication	No	No	No

*abbreviations : UPN=unit patient number, VOD=veno-occlusive disease, rt-PA=recombinant tissue-plasminogen activator

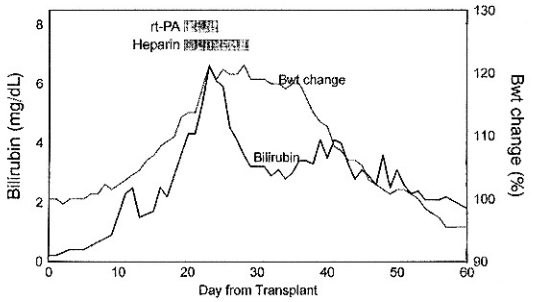

Fig. 1. Clinical course of VOD in UPN 1

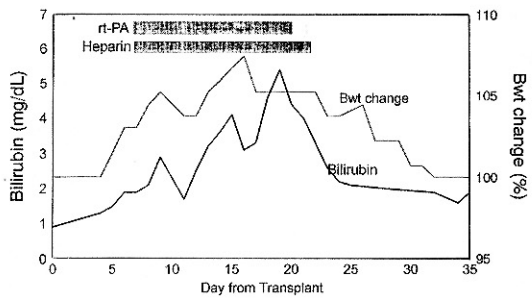

Fig. 2. Clinical course of VOD in UPN 2

UPN 1 had jaundice (serum total bilirubin 4.3 mg/dL), renal insufficiency (serum creatinine 3.0 mg/dL), ascites and weight gain refractory to diuretic therapy, and tender hepatomegaly at the start of rt-PA administration. Serum creatinine level began to decrease within 24 hours of the first dose, and bilirubin level within 4 days. Fluid retention such as ascites and weight gain improved slowly, but was eventually returned to baseline state (Fig. 1). UPN 2 suffered from tender hepatomegaly and was mildly jaundiced since 4 days posttransplant, and gained body weight 3 % above baseline state at day 6 when rt-PA was administered. Body weight began to decrease at 10 days from the start of therapy, bilirubin at 13 days (Fig. 2). UPN 1 and 2 had complete resolution of signs and symptoms of VOD and are alive longer than 548 and 316 days posttransplant without evidence of VOD. UPN 3 had hyperbilirubinemia (total serum bilirubin 2.5 mg/dL), tender hepatomegaly, ascites, and weight gain at the start of rt-PA administration. Administration of heparin was discontinued at third day of the therapy because of prolongation of PTT, then resumed 2 days later. He received increased dosage of rt-PA (20 mg/day) 5 days from the start of therapy. His body weight declined to baseline state, but serum total bilirubin level did not return to normal value (Fig. 3). His clinical course of VOD was complicated by HCV infection which was diagnosed at day 106 when he was found to be seropositive for antibody to HCV. He is alive at longer than 111 days posttransplant with residual hepatic dysfunction that consists hyperbilirubinemia, elevation of serum alkaline phosphatase, and seropositivity to HCV.

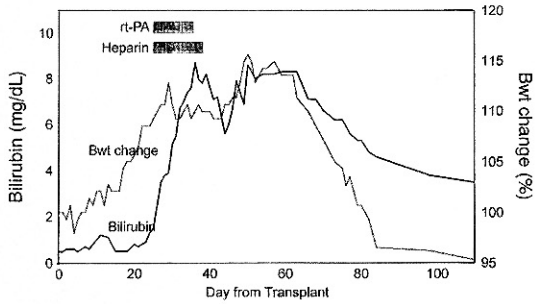

Fig. 3. Clinical course of VOD in UPN 3

During the rt-PA treatment days, there was no significant hemorrhagic complications. Engraftment was evident at 11 to 36 days posttransplant with neutrophil counts higher than 500/mm^3.

DISCUSSION

Pathogenesis of VOD of the liver is a fibrous obliteration of hepatic venules causing postsinusoidal obstruction and intrahepatic portal hypertension (Zafrani et al., 1983). The disorder was originally described in patients with chemically-induced toxic injury to the liver (Stuart and Bras, 1957). It is now usually associated with chemoradiotherapy, particularly with myeloablative therapy in combination with BMT (Shulman and Hinterberger, 1992). With infection and GVHD, it is the major cause of mortality and morbidity in allogeneic BMT (McDonald et al., 1984). The clinical features of VOD are initially due to intrahepatic portal hypertension and typically develop within 21

days posttransplant (Shulman et al., 1980). Although the diagnosis of VOD can only be confirmed by histological examination, this is often not possible in patients undergoing BMT because the onset of the disease occurs during a period of profound thrombocytopenia. Given this difficulty, the primary diagnosis is usually made on strictly defined clinical criteria. Clinical criteria for a diagnosis of VOD have been developed by both the Seattle and Baltimore groups. According to the Seattle criteria, two of the three clinical manifestations (jaundice and painful hepatomegaly or fluid retention) must be present by 20 days posttransplant (McDonald et al., 1993). The Baltimore criteria include jaundice (bilirubin $\geq$ 2.0 mg/dL) and two of the following : hepatomegaly (usually painful), ascites, or $\geq$ 5 % weight gain (Jones et al., 1987). The positive predictive values for both criteria are 88 % or more (Baglin et al., 1994). We used the Seattle criteria for diagnosis of hepatic VOD, but all three patients in this study met both criteria.

Several groups have reported various factors associated with development of VOD after BMT, the most proximate of which is the preparative regimen (Bearman, 1995). The incidence of severe VOD is higher following conditioning with cyclophosphamide (CY)/total body irradiation (TBI) when the dose of TBI is greater than 10-12 Gy (McDonald et al., 1993). Use of regimens that contain busulfan (BU) has been associated with a high incidence of VOD, particularly when BU doses exceed 16 mg/kg (Meresse et al., 1992). Three randomized trials of BU/CY versus CY/TBI have recently reported. In one study, VOD occurred infrequently in either treatment arm (Blaise et al., 1992). Another study reported that the probability of developing VOD was significantly greater in the group randomized to busulfan (Ringden et al., 1994). However a more recent randomized trial from Seattle did not show VOD to be more common in transplant recipients prepared with BU/CY (Clift et al., 1994). Statistical analyses have identified additional independent risk factors for VOD. The contradictory results of these analyses reflect variations in study design, definitions of VOD, patient population, and preparative regimens, making comparison of the data difficult. The most important of these additional risk factors are pretransplant liver disease including hepatitis C, elevated transaminase level at the time of transplant, persistent fever and antibiotic use in the early preconditioning and postconditioning period, BMT from mismatched or unrelated donors, and use of methotrexate for GVHD prophylaxis (McDonald et al., 1993 ; Frickhofen et al., 1994 ; Shuhart and McDonald, 1994 ; Bearman, 1995). All three patients with VOD in this study had some risk factors. All patients were prepared with BU/CY for transplant, and received methotrexate/cyclosporine for GVHD prophylaxis. UPN 1 and 2 were hepatitis B virus carrier, and UPN 3 had history of drug-induced hepatitis and elevated ALT level at the time of transplant. Hepatitis B virus antigen was positive in two of three patients with VOD compared to five patients without VOD in whom only one patient was a hepatitis B virus carrier and three had antibodies to hepatitis B virus. Four patients who received heparin prophylaxis did not develop VOD, and it is suggested that heparin prophylaxis may be effective in prevention of VOD.

Given that the pathogenesis of VOD is likely multifactorial, studies aimed at its prevention can approach the disease in several ways. Conditioning regimens can be altered to limit liver toxicity, whereas drugs that affect coagulation, venous patency, and cytokine release can be administered prophylactically. A number of clinical trials have been conducted with this intent and several agents have been evaluated. The results of these prophylactic trials have been contradictory (Shuhart and McDonald, 1994). In our institution, pentoxiphylline and/or ursodeoxycholic acid had been used for the prevention of VOD. However, a randomized trial of pentoxifylline showed no benefit over placebo, and only a small trial was reported regarding efficacy of ursodeoxycholic acid.

The prognosis of VOD is variable ranging from complete recovery to fulminant hepatic failure and death. Published case fatality rates for BMT-related VOD range from 0 to 67 % (Shuhart and McDonald, 1994). These figures are dependent on how each center defines both VOD and fatal VOD. A mathematical model that predicts severity of VOD based on the rate of increase of bilirubin levels and weight has been published (Bearman et al, 1993). If a discrimination is possible between patients who are likely to develop severe VOD and those whose illness is likely to be self-limited, patients who are likely to develop severe VOD could be treated early in the hope that early intervention might alter the natural history of VOD and prevent death caused by VOD. Theoretically, when thrombosis is already present, thrombolytic therapy may relieve intrahepatic obstruction and restore liver blood flow whilst endothelial healing takes place. For that reason, the use of a thrombolytic agent could

be a rational approach to the treatment of VOD.

There is no effective therapy for VOD that has been evaluated in a prospective randomized fashion. Treatment of established VOD is initially supportive with maintenance of intravascular volume and management of hepatic failure (Baglin, 1994). A number of specific therapeutic maneuvers have recently been attempted for progressive VOD. Several trials of PGE1 for VOD showed contradictory results (Bearman, 1995). Surgical decompression of portal hypertension by porto-caval shunting and successful orthotopic liver transplantation have been achieved (Shuhart and McDonald, 1994). Major surgery is, however, particularly hazardous in these patients who are severely immunosuppressed even though the operation is technically successful.

Recently rt-PA has been used in patients with established VOD (Baglin et al., 1990 ; Bearman et al., 1992 ; Laporte et al., 1992 ; Ringden et al., 1992 ; Rosti et al., 1992 ; Yu et al., 1994). A total 15 patients have been reported in the literature (Table 4). rt-PA was administered at a dose of 10 to 50 mg per day for 2 to 7 days. On the whole, ten of fifteen patients responded to rt-PA. rt-PA was first used in a patient with multiple myeloma who developed VOD on day 25 after an autologous transplant using BU/CY (Baglin et al., 1990). He was treated with 50 mg of rt-PA daily for four consecutive days and liver function tests improved within 48 hours. There have been concerns that treatment with rt-PA in a patient population already profoundly thrombocytopenic might lead to bleeding. In a report of Seattle, seven patients, who had developed severe VOD, were treated with 10 mg of rt-PA daily administered over two consecutive days and a continuous infusion of heparin (Bearman et al., 1992). In an animal study, the combination of rt-PA and heparin was significantly better than rt-PA alone for arterial and venous thrombolysis (Rapold et al., 1991). Five patients in the report of Bearman et al., responded to therapy, and no patient had significant hemorrhagic complications with rt-PA. In another report, however, two patients who were treated with rt-PA at a dose of 50 mg per day for 3 and 7 days developed catastrophic bleeding complications (Ring-

Table 4. Published data on therapy with rt-PA for VOD

	Age	Dx	Proparative regimen	Transplant type	Onset of VOD (day)	rt-PA				Heparin	Major bleeding complications
						start (day)	dose (mg/d)	duration (days)	response		
1)Baglin	45	MM	BU-CY	autologous	25	30	50	4	good	no	no
2)Laporte	45	CML	BU-CY	allogeneic	7	15	50	4	good	no	no
3)Rosti	43	MM	BU-CY	allogeneic	13	35	50	4	good	no	no
4)Bearman	43	CML	BU-CY	allogeneic	8	16	10	2	good	yes	no
	30	MM	BU-CY	allogeneic	2	9	10	2	good	yes	no
	43	CML	CY-TBI	allogeneic	2	18	10	2	good	yes	no
	53	CML	BU-CY	allogeneic	1	8	10	2	good	yes	no
	36	ALL	CY-TBI	allogeneic	1	4	10	2	good	yes	no
	57	ALL	CY-TBI	allogeneic	2	9	10	2	poor	yes	no
	23	ALL	CY-TBI	allogeneic	1	6	10	2	poor	yes	no
5)Ringden	32	CML	CY-TBI	allogeneic	10	13,27$	50	4,3$	poor	no	tracheal bleeding
	46	AML	BU-CY	allogeneic	7	29	50	3	poor	no	ICH
6)Yu	20	AML	BU-CY	autologous	5	7	0.25-0.5#	4	good	no	no
	18	ALL	CyA-TBI	autologous	7	10	0.25-0.5#	4	poor	no	no
	17	AML	BU-CY	autologous	24	4	0.25-0.5#	4	good	no	no
7)Lee@	22	CML	BU-CY	allogeneic	8	20	10	7	good	yes	no
	41	CML	BU-CY	allogeneic	4	6	10	14	good	yes	no
	34	ALL	BU-CY	allogeneic	10	26	10→20	11	good	yes	no

* abbreviations : VOD=veno-occlusive disease, rt-PA=recombinant tissue-plasminogen activator, Dx=diagnosis, MM=multiple myeloma, CML=chronic myelogenous leukemia, ALL=acute lymphoblastic leukemia, AML=acute myelogenous leukemia, BU-CY=busulfan+cyclophosphamide, CY-TBI=cyclophosphamide+total body irradiation, CyA-TBI=cyclophosphamide+cytosine arabinoside+total body irradiation, ICH=intracranial hemorrhage

mg/kg/day

$ rt-PA was reinstituted at day 27 with 50 mg/day given for additional 3 days.

@ this report.

den et al., 1992). We administered rt-PA at a dosage of 10 mg per day except one patient (UPN 3), who received increased dosage of rt-PA (20 mg per day) since 5 days from the start of therapy, and there was no significant bleeding complication. We also administered heparin concomitant with rt-PA at a dosage of 10,000 U per day. All three patients responded to rt-PA and liver function returned to normal in two patients. rt-PA was administered over more days in our patients compared to previous reports. Prolonged administration of rt-PA was feasible without bleeding episode, and it seems that rt-PA may alter the natural course of VOD. The benefit of prolonged administration of rt-PA in our study, however, was not clear. Further studies are warranted to determine the dosage, duration of treatment, indication, efficacy, and bleeding complications.

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