Successful Treatment with Defibrotide for Sinusoidal Obstruction Syndrome after Hematopoietic Stem Cell Transplantation

KIMIKAZU YAKUSHIJIN, TOSHIMITSU MATSUI, ATSUO OKAMURA, KATSUYA YAMAMOTO, MITSUHIRO ITO, and KAZUO CHIHARA

Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine

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Sinusoidal obstruction syndrome (SOS) (formerly known as hepatic veno-occlusive disease (VOD)) is a life-threatening complication subsequent to hematopoietic stem cell transplantation. However, no completely satisfactory strategies for the treatment of SOS have been established yet. Defibrotide is a single-stranded polydeoxyribonucleotide with anti-thrombotic, anti-ischemic, anti-inflammatory and thrombolytic properties, but without systemic anticoagulant effects, and some encouraging results have been reported in western countries. We treated four patients with defibrotide for SOS, since there seemed to be no possibility to cure the patients with conventionally available treatments in Japan. All patients showed evidence of multiple organ failure at the start of the treatment. Defibrotide was administered intravenously in normal saline in four divided doses for 14 to 27 days. Three patients (75%) responded to the therapy, while one died of SOS and cytomegalovirus infection despite intensive therapy. None of the patients suffered from significant adverse effects such as severe hemorrhage. This is the first report dealing with the treatment with defibrotide of Japanese patients with SOS. Because defibrotide is considered to be promising for the treatment of SOS, it is important to start a phase II study as soon as possible.

In the 1950s, the term “veno-occlusive disease” (VOD) was used to describe obliterative fibrosis within small hepatic venules observed by light microscopy (5). Cases of hepatic VOD at that time were not associated with hematopoietic stem cell transplantation (HSCT), but now it is known as a life-threatening complication after HSCT in regimen-related toxicities (RRT). The liver injury originates in the hepatic sinusoids, and the involvement of hepatic veins is not essential to the development of hepatic VOD (10,32). Thus the term “sinusoidal obstruction syndrome” (SOS) has been proposed as a more appropriate designation for hepatic VOD (11).

SOS usually occurs within the first 3 weeks after HSCT as a result of endothelial and hepatic damage caused by the conditioning regimen (2,3,21,33). It is characterized by painful hepatomegaly, jaundice, ascites and unexplained weight gain. Poor hematological recovery and platelet transfusion-refractory thrombocytopenia makes it difficult to conduct...
percutaneous liver biopsy, so that the diagnosis of SOS is made on the basis of clinical diagnostic criteria (18,20,21). The reported incidence of SOS is 5.3% to 54% (7,18,21,23,26). Various attempts at treatment of SOS have used prostaglandin E1 (17), tissue plasminogen activator (tPA) and heparin (1,4), antithrombin III (ATIII) (14,22), and others. However, no completely satisfactory strategies for the treatment of SOS have been established yet.

Defibrotide is a single-stranded polydeoxyribonucleotide extracted from mammalian tissue with anti-thrombotic, anti-ischemic, anti-inflammatory and thrombolytic properties, but without associated significant systemic anticoagulant effects (25). Although some encouraging results have been reported in western countries (9,27,28), defibrotide is not usually available in Japan. This paper is the first report dealing with four Japanese patients who met the clinical criteria for SOS and were treated with defibrotide on compassionate grounds at our hospital.

**PATIENTS AND METHODS**

**Patients.** From March 2003 through August 2005, four patients with SOS were treated with defibrotide (Crinos S.p.A., Milan, Italy) on compassionate grounds at our hospital. The diagnosis of SOS was established clinically based on the occurrence of two of the following events within 20 days of transplantation: hyperbilirubinemia (>2.0mg/dl), hepatomegaly or right upper quadrant pain of liver origin, and sudden weight gain (>2% of baseline body weight) because of fluid accumulation (the “Seattle criteria”) (21). The written informed consents were obtained from the patients and their families. Defibrotide was emergently imported with the approval of the Ministry of Health, Labour and Welfare in Japan.

**Patient monitoring and evaluation.** Total serum bilirubin, serum creatinine, blood urea nitrogen (BUN), body weight, complete blood count (CBC), fibrinogen, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were monitored during therapy. Time of onset of SOS was defined as the day that the retrospective chart review confirmed that the patient met the diagnosis criteria. Multiple organ failure (MOF) was diagnosed, if there was documented dysfunction of one other system besides the liver. Renal dysfunction was defined as a doubling of the baseline creatinine or dialysis dependence. Pulmonary dysfunction was defined by the need for supplemental oxygen and/or documentation of hypoxemia by arterial blood gas measurement or oxygen saturation by means of oximetry, or the need for mechanical ventilation. Central nervous system dysfunction was defined by the documentation of confusion, lethargy, delirium, and/or coma (27).

**Treatment Design.** Defibrotide was administered intravenously in normal saline in four divided doses of 10mg/kg-40mg/kg, infused daily over 2 hours. Defibrotide was increased incrementally if the response was slow or poor and discontinued or reduced if significant toxicities due to defibrotide were encountered. The planned treatment course was for a minimum of 14 days, and if complete response as defined below was achieved, defibrotide was tapered off. During therapy, platelet transfusion was administered when the platelet count was less than 20,000/μL, and red blood cell transfusions were used to keep hemoglobin at more than 6.0g/dl. If necessary, fresh frozen plasma (FFP) was also transfused to maintain the fibrinogen level at more than 150mg/dl or PT at more than 30%.

**Definition of response.** Complete response (CR) was defined as bilirubin decreasing to <2.0mg/dl and the complete resolution of all other end-organ dysfunctions. Partial response (PR) was defined as a reduction in bilirubin but persistence or occurrence of other end-organ
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toxicities. Any patient who failed to achieve CR or PR was defined as having no response (NR) (9).

Classification of SOS. The severity of SOS was defined according to the established criteria: mild for clinically manifested SOS that resolved without intervention; moderate for SOS that required treatment but resolved completely; and severe for SOS that caused death or progressed to multiple organ failure (21).

RESULTS

Case 1

In February 1998, a 58-year-old man was diagnosed with diffuse large B-cell lymphoma (Stage IV). He achieved complete remission (CR) after undergoing three cycles of chemotherapy (CHOP: cyclophosphamide, adriamycin, vincristine and prednisone) followed by involved field irradiation to the primary lesion in the right maxillary sinus. In October 2002, new multiple lesions in the stomach appeared. After additional three cycles of CHOP, the second CR was confirmed. The patient then received etoposide (500mg/m²) for four days, followed by peripheral blood stem cell (PBSC) harvest. After additional CHOP, high dose chemotherapy consisting of ranimusutine (200mg/m²) for 2 days, carboplatin (300mg/m²) for 4 days, etoposide (500mg/m²) for 3 days and cyclophosphamide (50mg/kg) for 2 days (MCVC) was performed, followed by PBSC transplantation (PBSCT) in March 2003. The number of CD34+ cells infused was 4.2 x 10⁶ cells/kg. On day +6, the total serum bilirubin began to elevate, and reached 2.8mg/dl with 7% weight gain from baseline on day +7. A diagnosis of SOS was followed by administration of dalteparin sodium at a dose of 5000U per day by means of continuous infusion with 600mg of ursodeoxycholic acid (UDCA). ATIII at a dose of 1500U per day was also used because the level was as low as 50%. Engraftment of both neutrophils and platelets was achieved on day +10. On the same day, pleural effusion, ascites, and renal dysfunction were noted. As liver dysfunction progressed, tPA at a dose of 400,000U/day was administered for 6 days after informed consent, but had no effect. On day +20 he needed supplemental oxygen, and, as total bilirubin had increased to 22.3mg/dl by day +22, bilirubin absorption was performed for three days. Nevertheless, MOF became aggravated. Defibrotide was administered from day +25, and after total bilirubin had increased to 26.7mg/dl on day +30, and it began to decrease gradually. The patient’s overall condition also began to improve. However, the reduction in total bilirubin stopped on day +34, and the defibrotide dose was augmented to 2800mg per day. In addition, cytomegalovirus (CMV) pneumonitis developed on day +35, and despite the introduction of antiviral therapy with ganciclovir, he died on day +41. Autopsy showed that the cause of death was SOS and CMV pneumonitis.

Case 2

In December 2003, a 33-year-old woman was diagnosed with acute myeloid leukemia (M4). In spite of two cycles of remission induction chemotherapy, not even hematological CR was achieved. After the administration of low dose chemotherapy, including cytarabine in order to suppress the increase in leukemic cells, a conditioning regimen consisting of 12Gy of total body irradiation (TBI) with 50mg/kg of high dose cyclophosphamide (CY) for 2 days was performed, followed by umbilical cord blood transplantation (CBT). The unit was 1-locus HLA mismatched for this patient, and 2.5 x 10⁷ cells/kg of nucleated cells were infused. Cyclosporine A (CyA) and short-term methotrexate (MTX) were used for graft-versus-host disease (GVHD) prophylaxis. On day +14, pitting edema of the legs and elevation of serum total bilirubin were noted, and the patient reported experiencing right
upper quadrant pain. As SOS was suspected, dalteparin sodium was administered at a dose of 3500U per day by means of continuous infusion with 600mg of UDCA. ATIII at a dose of 1500U/day was also used because the level was as low as 42%. On day +16, total bilirubin had reached 2.4mg/dl accompanied by renal dysfunction and 3.4% weight gain from the baseline. The diagnosis of SOS was followed immediately by the initiation of defibrotide administration at a dose of 480mg a day, but because of poor response, the dose was increased to 1200mg daily. The patient’s general condition then gradually ameliorated and neutrophil engraftment was achieved on day +26. On day +32, the total bilirubin level had fallen to 1.0mg/dl, and defibrotide was tapered from day +34. Since no deterioration of SOS was observed, defibrotide could be stopped and complete response was achieved on day +42. The findings of bone marrow aspiration performed on day +39 showed complete remission, and the donor-recipient chimerism analysis showed a 100% donor pattern.

**Case 3**

In April 2001, a 51-year-old man was diagnosed with acute myeloid leukemia (M3). The first complete remission was achieved as a result of chemotherapy with all-trans retinoic acid (ATRA), but relapse was confirmed during the maintenance chemotherapy. Re-induction chemotherapy initiated in June 2003 could achieve only hematological CR even after the additional chemotherapy. The conditioning regimen consisted of TBI and CY as described in the preceding case history, followed by CBT in June 2004. The unit was 2-loci HLA mismatched for the patient, and 2.2 x 10^7 cells/kg of nucleated cells were infused. CyA and short-term MTX were used for GVHD prophylaxis, but because of graft failure, the second CBT was performed on day +39. The conditioning regimen consisted of 30mg/m^2 of fludarabine for 6 days and 4mg/kg of busulfan for 2 days. The unit was 2-loci HLA mismatched, and the number of infused nucleated cells was 2.0 x 10^7 cells/kg. This time, CyA and mycophenolate mofetil (MMF) were used for GVHD prophylaxis. Because of high-grade fever, skin rash, and diarrhea, glucocorticoid was administered on day +10 of the second CBT, in view of the so-called “pre-engraftment reaction”. The patient’s clinical condition continued to deteriorate and oxygen support was required. On day +19 of the second CBT, total bilirubin was elevated at 3.0mg/dl and ultrasonography showed mild hepatomegaly. The presence of renal dysfunction, generalized edema and delirium was also established. Neutrophil engraftment was achieved on day +32, but the overall condition never improved. Because hepatic GVHD could not be completely ruled out, administration of glucocorticoid was continued in combination with 600mg of UDCA. Since total bilirubin in association with hepatomegaly was 8.2mg/dl, the criteria for SOS had been met, defibrotide was started at a dose of 800mg daily from day +33. Because of poor response, the dose of defibrotide was increased to 1200mg daily. By day +42 total bilirubin had decreased to 7.2mg/dl, but the patient’s overall condition deteriorated. When hematochezia occurred in association with CMV antigenemia, CMV colitis was strongly suspected, and the antiviral therapy with ganciclovir was initiated. However, the patient died on day +59 after the second CBT. Autopsy showed severe hepatic GVHD and the disappearance of SOS. Hematochezia was caused by the lesion of ileum due to CMV infection and thrombotic microangiopathy (TMA).

**Case 4**

In January 2005, a 45-year-old man was diagnosed with chronic myeloid leukemia in the accelerated phase. Imatinib mesylate at a dose of 400mg was administered, but was not effective. Two months later, the occurrence of lymphoid blast crisis prompted the initiation
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of combination chemotherapy with vincristine and prednisone. Although the treatment proved to be very effective in the bone marrow, leukemia relapse occurred in the central nervous system. Intrathecal chemotherapy consisting of MTX (15mg), cytarabine (40mg), and dexamethasone (4mg) was administered a total of 5 times. Prior to the conditioning regimen, 12Gy of whole brain irradiation was performed. The conditioning regimen consisted of TBI and CY, followed by bone marrow transplantation (BMT) from an HLA-matched unrelated donor. Tacrolimus and MMF were used for GVHD prophylaxis. 2.7 x 10^8 cells/kg of nucleated cells with 2.5 x 10^6 cells/kg of CD34+ cells were infused. On day +8, the patient experienced right upper quadrant abdominal pain and tenderness and showed a weight gain of 6.8% accompanied by renal dysfunction. Ultrasonography showed hepatomegaly, enlarged portal vein diameter and ascites. Although total bilirubin was 1.3mg/dl, a diagnosis of SOS was established, and defibrotide at a dose of 1200mg was started in combination with 600mg of UDCA. On day +13 renal dysfunction and liver dysfunction began to improve, neutrophil engraftment was achieved on day +18 and on day +22, complete response to defibrotide was achieved. From day +24, defibrotide was tapered off without any deterioration in the patient’s overall condition. As intrathecal chemotherapy was performed repeatedly after BMT, platelet engraftment was achieved later. Three months after the onset of SOS the patient is in good clinical condition without any liver dysfunction or relapse of CML.

Data were summarized from the retrospective review of the medical charts and laboratory findings for four patients who received defibrotide for treatment of SOS after HSCT at our hospital.

**Patient characteristics.** Patient age ranged from 34 to 59 years with a median age of 54 years (Table 1). All four patients showed evidence of underlying hematological malignancy, one underwent autologous stem cell transplantation (SCT) and others allogeneic SCT, two of whom underwent CBT. The patient undergoing autologous SCT received MCVC, and those treated with allogeneic SCT except case 3 underwent TBI and CY. Patient 3 had previously been administered a preparative regimen of TBI and CY. Subsequently the patient was treated with reduced-intensity stem cell transplantation (RIST) consisting of fludarabine and busulfan. Several different GVHD prophylaxis regimens were used.

**Clinical features.** All patients met the Seattle criteria for SOS (Table 2). Median time of onset of SOS was on day +12 (range, 7 – 19), and the median bilirubin at the onset of SOS was 2.6mg/dl (range, 1.3 – 3.0).  

**Patient condition and Outcome.** All patients achieved neutrophil engraftment, and three platelet engraftment (Table 3). All of them suffered from renal dysfunction, and two cases of severe SOS with pulmonary dysfunction had a fatal outcome (Table 4). The administered daily dose of defibrotide varied widely, while none of the patients had to discontinue defibrotide administration because of significant adverse effects. CR was clinically observed in two patients. Case 3 died of acute GVHD, TMA of ileum, and CMV infection, but not of SOS and case 1 of SOS and CMV infection. However, a transient reduction in the latter’s total bilirubin suggested a certain effect of defibrotide on SOS. Thus, three of the four patients with SOS were considered to have responded to defibrotide therapy.
TABLE 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Type of transplantation</th>
<th>Conditioning</th>
<th>GVHD prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59/Male</td>
<td>NHL</td>
<td>Auto (MCVC)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34/Female</td>
<td>AML (M4)</td>
<td>Allo (CBT) TBI-CY CYA/MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>53/Male</td>
<td>AML (M3)</td>
<td>Allo (CBT) Flu-BU CyA/MMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>55/Male</td>
<td>CML (CP2)</td>
<td>Allo (BMT) TBI-CY FK506/MMF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NHL indicates non-Hodgkin's lymphoma; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CP2, 2nd chronic phase; Auto, autologous peripheral blood stem cell transplantation; Allo, allogeneic stem cell transplantation; CBT, cord blood transplantation; BMT, bone marrow transplantation; MCVC, ranimustine/carboplatin/etoposide/cyclophosphamide; TBI, total body irradiation; CY, cyclophosphamide; Flu, fludarabine; BU, busulfan; N/A, not applicable; CyA, cyclosporine A; MTX, methotrexate; FK506, tacrolimus

TABLE 2. Clinical features.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset of SOS</th>
<th>T-Bil* (mg/dl)</th>
<th>Hepatomegaly</th>
<th>RUQ</th>
<th>%Wt*</th>
<th>Ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Day7</td>
<td>2.8</td>
<td>No</td>
<td>No</td>
<td>7.0%</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Day16</td>
<td>2.4</td>
<td>No</td>
<td>Yes</td>
<td>3.5%</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Day19</td>
<td>3.0</td>
<td>Yes</td>
<td>No</td>
<td>&lt;2%</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Day8</td>
<td>1.3</td>
<td>Yes</td>
<td>Yes</td>
<td>6.8%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* at onset of SOS
RUQ, right upper quadrant; Wt, body weight.

TABLE 3. Patient condition.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Day of Neutrophil engraft</th>
<th>Day of Platelet engraft</th>
<th>Evidence of MOF</th>
<th>Evidence of cause other than SOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Day 10</td>
<td>Day 10</td>
<td>R, L</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Day 26</td>
<td>Day 53</td>
<td>R</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Day 32</td>
<td>NA</td>
<td>R, L, E</td>
<td>Acute GVHD</td>
</tr>
<tr>
<td>4</td>
<td>Day 18</td>
<td>Day 89</td>
<td>R</td>
<td>No</td>
</tr>
</tbody>
</table>

NA, not achieved; MOF, multi-organ failure; R, renal dysfunction- doubling of the baseline creatinine; L, hypoxia requiring oxygen support; E, evidence of CNS encephalopathy

TABLE 4. Outcome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Therapy Duration</th>
<th>Dose of DF (mg)</th>
<th>Long-term response</th>
<th>Severity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 days</td>
<td>600-2800</td>
<td>NR</td>
<td>S</td>
<td>Dead: d +41 Autopsy: MOF, SOS, CMV infection</td>
</tr>
<tr>
<td>2</td>
<td>27 days</td>
<td>480-1200</td>
<td>CR</td>
<td>Mod</td>
<td>Dead: d +127. Relapse of AML</td>
</tr>
<tr>
<td>3</td>
<td>26 days</td>
<td>800-1200</td>
<td>NR</td>
<td>S</td>
<td>Dead: d +59 after 2nd CBT Autopsy: aGVHD, TMA of ileum, CMV infection No evidence of SOS</td>
</tr>
<tr>
<td>4</td>
<td>19 days</td>
<td>1200</td>
<td>CR</td>
<td>Mod</td>
<td>Alive: d +106</td>
</tr>
</tbody>
</table>

DF, defibrotide; CR, complete response; NR, no response; S, severe; Mod, moderate; CMV, cytomegalovirus; aGVHD, acute graft-versus-host disease; TMA, thrombotic microangiopathy
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DISCUSSION

SOS is one of lethal complications subsequent to HSCT. In cases of severe SOS, it is notoriously difficult to cure. Here, we described the usefulness of defibrotide for SOS after HSCT.

Encouraging reports regarding defibrotide have been published (9,27,28). Complete response was seen in more than one-third of the cases, and even poor-risk patients with MOF were expected to achieve complete response without severe toxicities. Mild to moderate toxicities such as nausea, transient mild systolic hypotension, fever, abdominal cramping, and vasomotor system troubles were reported, all of which are already known as side effects of defibrotide (25,28). In our cases, no severe adverse events were attributable to defibrotide, and it was especially effective in cases 2 and 4, leading to CR of SOS. The dramatic improvement in SOS during defibrotide therapy was encouraging because without defibrotide, the same cases would have been classified as “severe SOS”. In case 3, autopsy showed that SOS had disappeared, which could mean that defibrotide was effective for SOS. Even in case 1 with no response for tPA, defibrotide produced a transient improvement in the patient’s overall condition, which suggests that defibrotide may have had some effects. While the administered daily dose varied from 10 to 60mg/kg (9,27,28), even 20mg/kg of defibrotide could successfully prevent progression of SOS as shown in cases 2 and 4. However, it is certain that dose escalation of defibrotide may be required if there is a slow or no response to the starting dose. Taken together with the previous report (28), the starting dose should be 20mg/kg a day.

tPA is one of the other major modalities for the treatment of SOS. Combination therapy of tPA and heparin was successful for 29% of patients in one study, but was associated with a significant risk of life-threatening hemorrhage. The authors concluded that the treatment using tPA and heparin for patients with severe SOS who have already developed multiorgan dysfunction could not be recommended (4). In our case 1, we first used tPA before defibrotide administration, but it was not effective at all.

Some reports have described the use of ATIII for the treatment of multiple-organ dysfunction, including SOS after HSCT (14,24). However, the sample size of those studies was too small to determine the efficacy of ATIII concentrate. When an ATIII supplement was administered to our cases 1 and 2 because of a relatively low level of ATIII, no clinical improvement was seen even after administration of ATIII concentrate without defibrotide. The efficacy of ATIII concentrate thus remains anecdotal.

SOS constitutes a dose-limiting toxicity for a myeloablative conditioning regimen (21). It has been suggested that the incidence of SOS can be reduced with the use of minimally myelosuppressive conditioning such as 2Gy of TBI with or without fludarabine (16). A high incidence of SOS has been found to be associated with allogeneic transplantation, an increased serum aspartate aminotransferase (AST) level before cytoreductive therapy, high-dose conditioning, previous radiation therapy to the abdomen, and Karnofsky performance score of less than 90% before transplant (6). The AST level before conditioning of our cases was normal except in case 4, where it was a little higher than the normal upper limit (AST 35IU/l). In case 3, a reduced-intensity conditioning regimen consisting of fludarabine and busulfan was used, because the patient had previously undergone a myeloablative conditioning regimen including TBI and CY. The resultant damage to the endothelial cells may persist because of short-term conditioning regimens.

A tyrosine kinase inhibitor, imatinib mesylate was administered prior to HSCT in our case 4. It inhibits the vascular endothelial growth factor (VEGF) production (19) and affects the endothelial function. Although it has been reported that imatinib mesylate
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preceding HSCT does not increase acute transplant-related toxicities including SOS, the sample size of that study was relatively small (35). It is of great interest whether the administration of imatinib mesylate prior to HSCT triggered SOS. Gemtuzumab ozogamicin (GO), a calicheamicin-conjugated humanized anti-CD33 monoclonal antibody, is a new agent for acute myeloid leukemia. Some reports have suggested that there is an association between exposure to GO and the development of SOS (13,34). Prophylaxis as well as treatment for SOS after HSCT is thus very important. It has been reported that defibrotide administered in addition to heparin may prevent SOS (8), which seems to suggest that defibrotide should be used for prophylaxis of SOS depending on risk factors.

A diagnosis of SOS was established clinically on the basis of the Seattle criteria. However, the clinical features of SOS are non-specific, since there are other liver diseases that mimic SOS and are common after HSCT. We must therefore differentiate SOS from other causes such as cholangitis lenta, fungal liver disease, viral hepatitis, acute GVHD, medications and others (3,7). In this connection, the levels of serum plasminogen activator inhibitor-I (PAI-I) (30,31) and aminopropeptides of type III collagen (PIIIC) may be useful as biological markers of SOS (12,15,29). In our cases 1 and 2, total PAI-I level was as high as 246ng/ml and 55ng/ml, respectively, but an increase in PAI-I was also seen in a patient in septic shock after HSCT (30). It is thus very important to identify and detect more specific biological markers for diagnosis of SOS.

In conclusion, defibrotide should at present be considered a promising modality for the treatment of SOS. Although encouraging results have been reported in western countries, defibrotide has not been practically available in Japan. However, because defibrotide appears promising for the treatment of SOS, it is important to start a phase II study as soon as possible. In our experience, defibrotide was shown to be very effective for three of four SOS cases, which would have been fatal if treated with conventional modalities.

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