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RESEARCH ARTICLE

Early defibrotide therapy and risk factors for post-transplant veno-occlusive disease/sinusoidal obstruction syndrome in childhood

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Part of the study results was introduced in the abstract and presentation entitled "Efficacy of early defibrotide therapy for post-transplant VOD/SOS and risk factors in childhood" by the author at the 46th JSTCT Annual Meeting (JSTCT2024) of the Japanese Society for Transplantation and Cellular Therapy on March 23, 2024.

Abstract

Background: Veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a life-threatening complications of hematopoietic cell transplantation (HCT).

Methods: We studied the impact of early defibrotide (DF) therapy on the outcomes of pediatric patients with VOD/SOS after transplantation, focusing on recent immunotherapies. A total of 111 pediatric patients who underwent HCT for malignant disease between February 2017 and March 2023 at Kyushu University Hospital were included.

Results: Among 111 patients of less than 20 years of age who underwent HCT for malignancy at a single institution between 2017 and 2023, VOD/SOS occurred in 25 (23%) patients. VOD/SOS developed more frequently in the post-DF era (2020–2023, $n = 58$) than in the pre-DF era (31% vs. 13%, $p = .04$). The proportion of patients with relapsed/refractory acute lymphoblastic leukemia (ALL) was higher in the post-DF era than in the pre-DF era (44% vs. 8%, $p = .04$). Early DF therapy that was started at two European Society for Blood and Marrow Transplantation diagnostic criteria reduced the severity of VOD/SOS ($p < .01$) in comparison to non-early therapy started at less than two criteria. A multivariate analysis indicated that a history of cytokine release syndrome (odds ratio [OR] = 10.4, $p = .01$) and juvenile myelomonocytic leukemia (OR = 8.98, $p = .04$), but not an endothelial activation and stress index (EASIX) score of greater than 0.85, were independent risk factors for VOD/SOS.

Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval; CRS, cytokine release syndrome; DF, defibrotide; EASIX, the endothelial activation and stress index; EBMT, The European Society for Blood and Marrow Transplantation; HCT, hematopoietic cell transplantation; OR, odds ratio; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease.

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Conclusions: Early DF therapy improves the severity and survival outcomes of post-transplant VOD/SOS in children. However, its incidence is increasing in the era of immunotherapy for progressive diseases.

KEYWORDS

cytokine release syndrome, defibrotide, immunotherapy, VOD/SOS

1 | INTRODUCTION

Veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) is a potentially lethal complication of chemotherapy and/or hematopoietic cell transplantation (HCT) with a mortality rate of 60%–75%.¹ The diagnosis of VOD/SOS has been conventionally made according to the Baltimore² or Modified Seattle Criteria,³ including the triad of weight gain with or without ascites, hepatomegaly or painful hepatomegaly, and hyperbilirubinemia. The European Society for Blood and Marrow Transplantation (EBMT) proposed new criteria to facilitate the early diagnosis of VOD/SOS and earlier therapeutic intervention. These criteria include no limitation of the time of onset of VOD, no specific bilirubin cutoff level, a more objective assessment of ascites and hepatomegaly as well as the inclusion of refractory thrombocytopenia (RT) as a diagnostic criterion.^{4,5} The endothelial activation and stress index (EASIX) score is used as a predictive score for the development of VOD/SOS in adult patients.⁶ The validation of the EBMT criteria in pediatric cases has been progressing⁷; but these reports are limited, and the EASIX score has not been validated in pediatric cases.

Immunotherapy, including chimeric antigen receptor (CAR)-T cells, has been expanded to control refractory and/or relapsing hematologic malignancies in childhood.⁸ The advent of immunotherapy has changed the treatment strategy, including the indication and timing of HCT for refractory and/or progressive cases. Cytokine release syndrome (CRS) is a common complication of CAR-T therapy, and targeted immunotherapy, such as blinatumomab, shares the pathophysiological basis of endothelial injury with VOD/SOS.⁸ However, there is no information about the association between CRS and the development of VOD/SOS.

Defibrotide (DF) is currently the only treatment for VOD/SOS. It was approved for the treatment of VOD/SOS in post-HCT patients in Europe and the United States in 2013 and 2016, respectively.^{9,10} DF has been used to control non-thrombotic obstruction, thrombus formation, and fibrosis of the hepatic sinusoids.^{11,12} The efficacy of early administration of DF after the diagnosis of VOD/SOS is indicated by an expanded-access treatment program.¹³ DF prophylaxis has improved event-free survival,^{14,15} and appears to reduce the development of thrombotic microangiopathy (TMA) as an ominous complication of HCT.^{16,17} However, further discussions are needed to assess the utility of the prophylactic administration of DF.^{15,18} The therapeutic use of DF has been approved in Japan since 2019; however, the prophylactic use of DF has not been approved. The diagnostic criteria for VOD/SOS

have been established in adult cases to allow optimal interventions, but their utility in pediatric cases has not been evaluated.⁴ Although the Hok-US10 has been reported to standardize the diagnosis of VOD/SOS in childhood,¹⁹ abdominal ultrasound cannot be easily applied to pediatric patients with liver pain after HCT. Above all, evidence of the early effects of DF in childhood remains limited.

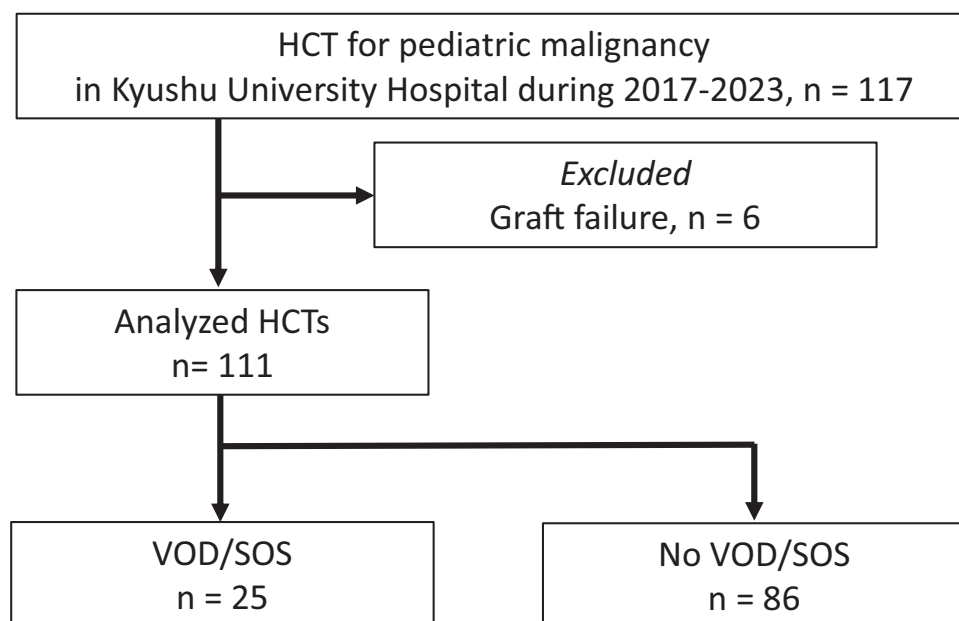
In the present study, we examined the clinical utility of DF therapy in pediatric patients in a cohort from a single institution, focusing on the EASIX score and immunotherapy. This observational study demonstrated the impact of early DF in pediatric cases, and for the first time, raised the risk of developing VOD/SOS in the era of CAR-T-cell therapy.

2 | SUBJECTS AND METHODS

2.1 | Study population

A total of 117 Japanese patients of ≤ 20 years of age underwent HCT for the treatment of malignant diseases at Kyushu University Hospital between January 2017 and March 2023 (Figure 1). This study enrolled 111 patients after excluding six patients with fatal graft failure. Among them, 25 were diagnosed with VOD/SOS based on the EBMT criteria. According to the approved use of DF in our hospital, patients were classified into two groups based on the time of HCT: pre-DF era group (2017–2019) and post-DF era group (2020–2023). In the pre- and post-DF eras, continuous infusion of low-molecular-weight heparin and oral ursodeoxycholic acid was performed for VOD/SOS prophylaxis from the pre-transplant period to approximately 1 month after transplantation.

In the pre-DF era, all patients who fulfilled the diagnostic criteria immediately received additional thrombomodulin alpha and symptomatic therapy without DF according to the protocol for adult cases. Sixteen patients (14.4%) achieved engraftment after repeated HCTs, with six graft failures and 10 relapses. VOD/SOS developed after HCT in 25 patients (23%). During the entire study period, we retrospectively classified patients into “early-DF therapy” and “non-early-DF therapy” groups if they received DF immediately after the fulfillment of two EBMT diagnostic criteria and more than two EBMT criteria of VOD/SOS, respectively (Table 1). This cutoff point was determined based on a consensus of three experts regarding the starting time of DF. Refractory thrombocytopenia was included in the two criteria for the early-DF therapy group. None of the patients with the two EBMT criteria achieved remission of VOD/SOS without treatment.



1. Changing incidence of VOD/SOS
2. Effect of early DF therapy on the severity and outcome
3. Risk factors for VOD/SOS

FIGURE 1 Flowchart of the defibrotide study. After excluding six patients, 25 of 111 patients were diagnosed with VOD/SOS based on the Seattle criteria. DF: defibrotide; HCT: hematopoietic cell transplantation; SOS: sinusoidal obstruction syndrome; VOD: veno-occlusive disease.

To assess the efficacy of DF therapy, the clinical variables of VOD/SOS cases were compared between the pre- and post-DF eras. A subanalysis was performed to compare the effect of early-DF therapy on the severity and outcome of VOD/SOS between early-DF and non-early-DF cases in the post-DF era. Furthermore, the risk factors for the development of VOD/SOS were investigated in all 111 patients, focusing on variables including the EASIX score, repeated HCT, conditioning, history of CRS treatment, and previous targeted immunotherapy. This study was approved by the ethics committee of Kyushu University (#23184-00) and was conducted in accordance with the institutional guidelines and the Helsinki Declaration.

2.2 | Statistical analysis

Fisher's exact test was performed for univariate analyses, while logistic regression analysis was performed for multivariate analyses. All analyses were performed using JMP (ver. 16.0; JMP Inc. SAS Institute).

3 | RESULTS

3.1 | Changing incidence of VOD/SOS

During the study period, the incidence of VOD/SOS tended to increase, whereas the number of HCTs remained stable. The backgrounds of the

25 patients did not differ to a statistically significant extent between the pre-DF and post-DF eras, with the exception of underlying disease; the percentage of patients with acute lymphoblastic leukemia (ALL) tended to be lower in the pre-DF era (Table 1). VOD/SOS occurred more frequently in the post-DF era than in the pre-DF era (18/58, 31% vs. 7/53, 13%; $p = .039$). Until May 2022, when the early-DF initiative started, 30% and 70% of patients fulfilled two EBMT criteria and more than two EBMT criteria, respectively, irrespective of the availability of DF. There were no significant differences in the severity or outcomes of VOD/SOS, TMA complications, or mortality (Table 2). No adverse events were observed in the patients with DF. Among the 25 patients with VOD/SOS, seven patients entered the intensive care unit for respiratory support, including four patients who received renal replacement therapy; however, no patients required peritoneal drainage.

3.2 | Effects of early-DF therapy on VOD/SOS

After the start of the early-DF initiative, the VOD/SOS peak grade was significantly reduced in comparison to the pre-DF era ($p = .04$). In the post-DF era, nine patients received early-DF therapy or non-early-DF therapy. Therefore, we compared the severity of VOD/SOS, complications of TMA, and patient outcomes. The ratio of grade 1–2 to 3–4 alone was significantly higher in patients who received early DF than in those who received non-early DF ($p < .001$, Table 2) without

TABLE 1 Patient characteristics in the pre-DF and post-DF eras.

	Total (n = 25)	Pre-DF era (n = 7)	Post-DF era		p-Value ^a
			2 EBMT criteria (n = 9)	>2 EBMT criteria (n = 9)	
Age at HCT^b	9, 0.6–19	3, 0.6–13	9, 2–19	10, 0.9–17	.09, .86
Sex, male/female	15/10	3/4	5/4	7/2	.38, .62
Primary disease					
ALL	13	2	5	6	
AML	3	0	1	2	
MPAL	1	0	1	0	
JMML	3	2	0	1	
T-AML	3	3	0	0	
DLBCL	1	0	1	0	
NB	1	0	1	0	.04, .49
State of remission					
1st CR	12	6	3	3	
2nd CR	6	1	2	3	
3rd CR	1	0	1	0	
Non-CR	6	0	3	3	.11, .75
Stem cells source					
rBMT/PBSCT	12	3	4	5	
uBMT/PBSCT	6	1	3	2	
CBT	6	3	1	2	
Auto-PBSCT	1	0	1	0	.73, .58
Donor type					
Haploidentical	2	0	1	1	
Non-haploidentical	23	7	8	8	.36, 1.00
Conditioning backbone					
TBI/CY or with VP	7	0	5	2	
TBI/FLU/MEL or with CY	10	5	2	3	
BU/MEL or with FLU	5	1	1	3	
BU/CY or with VP	3	1	1	1	.15, .48

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplantation; BU, busulfan; CBT, cord blood transplantation; CR, complete response; CY, cyclophosphamide; DF, defibrotide; DLBCL, diffuse large B-cell lymphoma; FLU, fludarabine; HCT, hematopoietic cell transplantation; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndromes; MEL, melphalan; MPAL, mixed phenotype acute leukemia; NB, neuroblastoma; PBSCT, peripheral blood stem cell transplantation; TBI, total body irradiation; VP, etoposide.

^aEach p-value is calculated between the pre-DF era and post-DF era or between 2 EBMT criteria and >2 criteria by Fischer's exact test.

^bAge is shown as the median and range (in years).

an obvious statistical bias (Table 1). The proportion of cases with increased serum bilirubin levels, but not transfusion-resistant thrombocytopenia, weight gain, hepatomegaly, or ascites, was significantly higher in patients with early DF ($p = .05$, Figure S3). All 18 patients in the post-DF era showed prodromal thrombocytopenia resistant to transfusion. The time from prodrome thrombocytopenia to the diagnosis (treatment) of VOD/SOS was shorter in the early-DF group than in the non-early-DF group ($p < .01$, Figure S4). Swimmer plot diagrams of patients who received early and non-early DF showed distinct VOD/SOS grades and outcomes (Figure S1A,B).

3.3 | Risk factors for the development of VOD/SOS

When we compared the variables between patients with and without VOD/SOS, the proportion of cases who received InO ($p = .03$) or who had a history of treatment for CRS ($p = .01$) was higher in patients with VOD/SOS (Table 3). No other variables differed between the groups. A logistic regression analysis was used to focus on covariates that have been reported as risk factors for VOD/SOS, including age less than 2 years,²⁰ juvenile myelomonocytic leukemia (JMML),²¹ non-complete response,²¹ busulfan-based regimen,²² sepsis,²¹ multiple HCT,²³

TABLE 2 Peak grade of VOD/SOS, complications of TMA, and outcomes in 25 patients.

	Total (n = 25)	Pre-DF era (n = 7)	Post-DF era (n = 18)		p-Value ^a	
			2 EBMT criteria (n = 9)	>2 EBMT criteria (n = 9)		
VOD/SOS severity						
Grade 1–2	9	1	8	0		
Grade 3–4	16	6	1	9	.36	<.001
TMA	2	0	0	2	1.00	.47
Cause of death						
VOD/SOS	5	2	0	3	.60	.21
Relapse	6	1	2	3	.64	1.00

Note: There is no significant difference in the distribution of patients between the pre-DF era and the >2 EBMT criteria group in the post-DF era. Abbreviations: DF, defibrotide; EBMT, European Society for Blood and Marrow Transplantation; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease.

^aEach p-value is calculated between the pre-DF era and post-DF era or between 2 EBMT criteria and >2 criteria by Fischer's exact test.

gemtuzumab ozogamicin (GO) or inotuzumab ozogamicin (InO),^{24,25} cord blood transplantation (CBT),²⁶ and EASIX score greater than 0.85.²⁷ In addition, a history of treatment for CRS was newly included in the analyses as a covariate. In the multivariate analysis, treated CRS (odds ratio [OR]: 10.4, 95% confidence interval [CI]: 1.69–64.1) and JMML (OR 8.98, 95% CI: 1.16–69.3) were identified as the only independent risk factors for the development of VOD/SOS (Table 4). CRS accounted for the increasing trend of VOD/SOS after immunotherapy, including CAR-T cells, in the post-DF era. The covariates used in this analysis are listed in Table 4. The median interval between CRS episodes and VOD was 130 days (range: 62–453 days).

4 | DISCUSSION

The present study revealed the benefit of early diagnosis of DF using the EBMT criteria in pediatric patients based on the severity and outcomes of VOD/SOS. An EASIX score of greater than 0.85 did not predict the development of VOD/SOS in this population. A history of treatment for CRS was notably indicated as an independent risk factor for the development of VOD/SOS, in addition to the known risk factor of JMML.⁶ The unique observation across the commencement of DF and immunotherapy, for the first time, corroborated an increasing trend of VOD/SOS in association with CAR-T cells raising the utility of DF prophylaxis in pediatric cases.

In the post-DF era, none of the nine patients with an early diagnosis of VOD/SOS died. In contrast, three of nine patients in the non-early-DF group died of VOD/SOS in the post-DF era, while two of seven patients in the non-early-DF group died from VOD/SOS in the pre-DF era. Before the early-DF initiative started, the proportion of early diagnosed cases was approximately equal, around 30%, in pre- and post-DF eras. This represented no grade bias at the time of the diagnosis. After the early-DF initiative, the proportion of grade 3–4 VOD/SOS cases decreased significantly during the course of treatment. These results verified that early initiation of DF improved the severity of VOD/SOS and subsequent transplant outcomes. The present study

was conducted in a high-volume center for pediatric malignancy, where the highest number of cases received HCT, CAR-T-cell therapy, and targeted immunotherapy over the past decade in Japan. Two patients were required to receive haploidentical HCT before remission, and both had VOD/SOS after 2020, with available DF and immunotherapy (Table 1). Haploidentical HCT without remission was reported to be a risk factor for the development and severity of VOD/SOS.²¹ The proportion of patients with relapsed or refractory ALL tended to be higher in the post-DF era than in the pre-DF era (Table 1). Eight patients had a treatment history of InO, blinatumomab, or CAR-T therapy during the development of VOD/SOS; however, none of the seven patients had this history in the pre-DF era ($p = .018$), suggesting a greater disease severity among the cases recruited in the post-DF era. In this setting, the higher incidence of VOD/SOS in the post-DF era might account for the increased number of cases of progressive disease in the post-DF era.

This study confirmed the diagnostic significance of refractory thrombocytopenia in children with VOD/SOS. Transfusion-resistant thrombocytopenia preceded any other symptoms of VOD/SOS in all patients (Figures S1A,B and S2). Previous studies on the pathophysiology of VOD/SOS indicated that thrombocytopenia arises from consumption involving endothelial cell activation,^{4,28} which is recognized as an indispensable finding of VOD/SOS in childhood.²⁹ However, ascites and bilirubin levels are not useful for making an early diagnosis. In our institution, abdominal ultrasound was not tested as a regular screening method, but was exclusively applied for suspected cases of VOD/SOS. A limited examination may not fully identify small amounts of ascites. According to the EBMT diagnostic criteria, transfusion-refractory thrombocytopenia, hepatomegaly, and weight gain were found at the diagnosis of VOD/SOS in 100%, 92%, and 92% of 25 cases, respectively.⁵ In addition, this study reported that elevated bilirubin levels (for 3 consecutive days or ≥ 2 mg/dL) and ascites were found in 88% and 76% of patients, respectively. VOD/SOS without overt jaundice has been more frequently reported in pediatric cases than in adult cases.⁵ Higher bilirubin levels are a poor prognostic factor in advanced VOD/SOS.³⁰ Taken together, this study verified

TABLE 3 Characteristics of patients with and without VOD/SOS.

	Total (n = 111)	VOD/SOS (n = 25)	No VOD/SOS (n = 86)	p-Value ^b
Age at HCT ^a	7.0, 0.6–19	9.0, 0.6–19	7.0, 0.7–18	.83
Sex, male/female	63/48	15/10	48/38	.82
Primary disease				
ALL	38	13	25	
AML	26	3	23	
MPAL	6	1	5	
JMML	6	3	3	
Lymphoma	12	1	11	
Solid tumors	12	1	11	
Other ^c	11	3	8	.11
State of remission				
1st CR	44	11	33	
2nd CR	31	5	26	
3rd CR	4	2	2	
Non-CR	32	7	25	.45
Stem cells source				
BMT	40	7	33	
CBT	29	6	23	
PBSCT	42	12	30	.47
Donor type				
Haploidentical	8	2	6	
Non-haploidentical	103	23	80	1.00
Conditioning				
Myeloablative conditioning	54	14	40	.50
BU-based conditioning	27	8	19	.22
Immunotherapy				
CAR-T cells	7	4	3	.04
Blinatumomab	11	5	6	.12
InO	9	5	4	.03
GO	3	0	3	1.00
Treated CRS ^d	10	6	4	.01

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplantation; BU, busulfan; CAR, chimeric antigen receptor; CBT, cord blood transplantation; CR, complete response; F, female; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; InO, inotuzumab ozogamicin; JMML, juvenile myelomonocytic leukemia; M, male; MDS, myelodysplastic syndromes; MPAL, mixed phenotype acute leukemia; PBSCT, peripheral blood stem cell transplantation.

^aAge is shown as the median and range (in years).

^bp-Values are calculated with Fischer's exact test.

^cOther: MDS, therapy-related AML, therapy-related MDS.

^dTreated CRS: cytokine release syndrome treated with dexamethasone, prednisolone, or tocilizumab.

that transfusion-unresponsive thrombocytopenia is a clue for the early diagnosis of pediatric VOD/SOS. The inflammatory response of hepatic sinusoidal endothelial cells leads to microvascular occlusion and sinusoidal blockage, which precedes the clinical and laboratory presentations of VOD/SOS.³¹ Pediatric cases of VOD/SOS have recently increased in challenging cases of HCT and/or CAR-T-cell therapy. With this trend, prophylactic DF for high-risk patients may be recommended to control VOD/SOS rather than the early administration of DF for selected patients with prodromal thrombocytopenia.

Prophylactic DF has recently been increasingly reported in adult patients.^{13,15,32} No TMA occurred in patients who received an early diagnosis of VOD/SOS in this study, whereas two non-early-DF group patients were complicated by and later died from TMA (Table 2). VOD/SOS and TMA are both associated with coagulopathy-related endothelial damage,³³ and the synergistic effect worsens post-transplant outcomes.^{34,35} Eculizumab has benefits in over half of pediatric patients with HCT-TMA.¹⁷ Prophylactic DF has also been reported to reduce the incidence of TMA after transplantation.¹⁶ The early-DF initiative might have had a preventive effect on the development of TMA and contributed to the subsequent decrease in mortality, although further verification in a larger number of cases is needed.

To maximize the effect of prophylactic DF, more information on high-risk cases is required. In this cohort, CRS treatment was identified as a novel risk factor for VOD/SOS. The number of pediatric cases of CAR-T-cell therapy has greatly increased to control relapsed and/or refractory ALL prior to HCT. CAR-T-cell-driven CRS often requires intensive care to control systemic inflammation³⁶ in association with endothelial dysfunction and hypercoagulability.^{8,37,38} VOD/SOS arises from the damage of sinusoidal endothelial cells and progressive venular occlusion.^{39,40} DF therapy may control CAR-T-cell-associated neurotoxicity, the etiological basis of which is linked to endothelial activation and disruption of the blood–brain barrier.³⁶ Indeed, CAR-T-cell-associated neurotoxicity was observed in one patient in the VOD/SOS group. Further studies are needed to clarify the effect of prophylactic DF on the development and outcomes of neurological complications after HCT in high-risk cases of VOD/SOS following CAR-T-cell therapy.⁴¹

The present study was associated with several limitations. First, it was a single-center retrospective study with a relatively small sample size. In Tables 1 and 2, the breakdown of patients into the pre-DF, and two and greater than two of EMBT criteria for statistical analyses with a small number of events lacked statistical power. Thus, there was a risk of obtaining p-values simply from multiple comparisons. In Table 4, some variables with nominal p-values and small sample sizes showed very broad 95% CIs. Second, the early diagnosis and DF initiative might have resulted in the overdiagnosis of mild VOD/SOS and overlooked cases with spontaneous resolution. The diagnostic criteria for pediatric EBMT are reportedly associated with a risk of overdiagnosis.⁴⁰ However, there was no bias in the patient backgrounds between the pre-DF and post-DF eras. The increasing number of cases at risk for VOD/SOS will clarify the utility of early DF as well as concerns related to its overdiagnosis. Third, in a limited number of cases, abdominal ultrasound may not have played a role in early screening to define liver

TABLE 4 Multivariable analysis of risk factors for VOD/SOS.

	VOD/SOS (n = 25)	No VOD/SOS (n = 86)	OR	Lower limit of 95% CI	Upper limit of 95% CI	p-value
Age <2 years	4	8	1.60	0.28	9.26	.60
JMML	3	3	8.98	1.16	69.3	.04
MAC	14	40	3.01	0.89	10.1	.08
BU	8	19	3.97	0.93	17.0	.06
GO/InO	5	7	1.32	0.22	7.97	.76
Multiple HCT	6	10	3.97	0.93	16.9	.06
Sepsis	6	10	2.34	0.58	9.41	.23
EASIX score >0.85	12	48	1.79	0.56	5.69	.32
Non-CR	7	25	0.17	0.10	1.50	.15
Treated CRS ^a	6	4	10.4	1.69	64.1	.01
CBT	6	23	0.67	0.20	2.23	.51

Note: A logistic regression analysis is performed as the multivariable analysis.

Abbreviations: BU, busulfan; CBT, cord blood transplantation; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; EASIX, endothelial activation and stress index; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; InO, inotuzumab ozogamicin; JMML, juvenile myelomonocytic leukemia; MAC, myeloablative conditioning; OR, odds ratio.

^aTreated CRS: cytokine release syndrome treated with dexamethasone, prednisolone, or tocilizumab.

images and the presence of ascites.^{19,42} Fourth, we did not analyze the effect of BU on conditioning regimens, because targeted BU levels were not monitored. Finally, in the early phase of the post-DF era, some patients may have waited until they met at least three items of the EBMT criteria before they started DF, this may have led to a potential bias of severity between the early-DF and non-early-DF group patients.

In conclusion, the utility of an early diagnosis and DF therapy has been demonstrated to improve the severity and outcomes of VOD/SOS in Japanese children. The earlier administration of DF may improve the outcomes of pediatric patients with VOD/SOS. Treatment requiring CRS as a risk factor for VOD/SOS may underpin the mechanism of systemic endothelial damage involving the biliary tract. Considering the genetic variation affecting endotheliopathy,^{43,44} early or prophylactic DF should be optimized according to the varied treatment history and genetic predisposition of pediatric patients undergoing HCT.

AUTHOR CONTRIBUTIONS

Hironori Goto and **Shunsuke Yamamoto** conceived and designed the study; acquired and analyzed the data; interpreted the data; and drafted the initial manuscript. **Yuhki Koga** and **Shouichi Ohga** conceived and designed the study; interpreted the data; and drafted the manuscript. **Utako Oba**; **Tamaki Ueda**; **Masataka Inoue**; **Yu Shimo**; **Satomi Yokoyama**; **Yusuke Takase**; **Wakako Kato**; **Souichi Suenobu**; and **Kenji Ihara** interpreted data. All authors critically reviewed the manuscript; approved the final version; and were accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest in association with the present study.

DATA AVAILABILITY STATEMENT

The datasets generated in this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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