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Incidence of Anicteric Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome and Outcomes with Defibrotide following Hematopoietic Cell Transplantation in Adult and Pediatric Patients

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Abstract

Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic cell transplantation (HCT) that is traditionally diagnosed using Baltimore or modified Seattle criteria. Whereas the Baltimore criteria require the presence of hyperbilirubinemia (bilirubin ≥2 mg/dL) for a diagnosis of VOD/SOS, the modified Seattle criteria do not. Before approval by the US Food and Drug Administration, defibrotide was available in the United States through an expanded-access study (T-IND). The T-IND protocol initially required post-HCT diagnosis of VOD/SOS by the Baltimore criteria or biopsy but was later amended to include patients diagnosed using the modified Seattle criteria. This post hoc analysis examined the incidence of VOD/SOS with a bilirubin level <2 mg/dL before and after Day 21 post-HCT in T-IND patients enrolled following the amendment allowing for diagnosis by the modified Seattle criteria. Survival of adult and pediatric patients with or without hyperbilirubinemia and with or without multiorgan dysfunction (MOD) was also evaluated. Of 803 post-HCT patients with VOD/SOS enrolled following the protocol amendment, 181 (23%) had a bilirubin level <2 mg/dL and would not have been diagnosed if hyperbilirubinemia was required. The bilirubin level at diagnosis was <2 mg/dL in 165 of 331 patients (50%) diagnosed by the modified Seattle criteria and in 16 of 23 patients (70%) diagnosed by biopsy. VOD/SOS with a bilirubin level <2 mg/dL was more common in pediatric patients (29%), although it also occurred

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in adult patients (15%). Patients with hyperbilirubinemia had lower Day 100 survival (54% versus 87% in patients with bilirubin <2 mg/dL) and a higher incidence of MOD (41% versus 26% in patients with bilirubin <2 mg/dL). The incidence of treatment-emergent adverse events and serious adverse events was lower in patients with a bilirubin level <2 mg/dL. These results indicate that anicteric VOD/SOS occurs in both adult and pediatric patients post-HCT and can be diagnosed before and after Day 21 in both groups. The worse survival in patients with bilirubin ≥2 mg/dL suggests that requiring hyperbilirubinemia may result in a progressed disease stage associated with worse outcomes. Taken together, these results highlight the importance of awareness and the possibility of VOD/SOS in the absence of elevated bilirubin level.

Keywords

Defibrotide; Anicteric; Veno-occlusive disease/sinusoidal obstruction syndrome; Bilirubin; Baltimore criteria; Modified Seattle criteria

INTRODUCTION

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic cell transplantation (HCT). It has a reported overall mean incidence of 8% to 14%, with an incidence of up to 60% in some high-risk populations [1–3]. VOD/SOS occurs as a result of activation and damage of the sinusoidal endothelium [4,5]. VOD/SOS with multiorgan dysfunction (MOD; renal and/or pulmonary) is reported to be associated with >80% mortality when treated with supportive care alone [1,6].

VOD/SOS is commonly characterized by hepatomegaly or right upper-quadrant pain, ascites, weight gain, and hyperbilirubinemia [7,8]. Traditionally, the Baltimore or modified Seattle criteria have been used to diagnose VOD/SOS [8–12]. Use of the Baltimore criteria requires the presence of hyperbilirubinemia (bilirubin ≥2 mg/dL) for diagnosis, whereas use of the modified Seattle criteria hyperbilirubinemia does not. In response to a need for earlier treatment of VOD/SOS, the European Society for Blood and Marrow Transplantation (EBMT) developed revised diagnostic and severity criteria separate for adults and children that acknowledge hyperbilirubinemia as a potential late finding in the progression of VOD/SOS in adults and as a frequent absence of VOD/SOS in children [7,8]. For adults, elevated bilirubin (≥2 mg/dL) is required for a diagnosis of VOD/SOS at ≤21 days post-HCT but not after Day 21 (late-onset VOD/SOS) [7,8]. The clinical literature suggests that VOD/SOS with bilirubin <2 mg/dL before Day 21 is uncommon in adults [8]. The highest risk for VOD/SOS is in children and, particularly, in infants [13]. For this high-risk population, elevated bilirubin is not required by the EBMT criteria, because approximately 30% of pediatric patients present with anicteric VOD/SOS (ie, bilirubin <2 mg/dL) [7].

In vitro, defibrotide has been shown to protect the endothelium from cytotoxic and inflammatory damage by ameliorating endothelial cell activation [14]. Evidence suggests that defibrotide restores thrombotic-fibrinolytic balance by promoting profibrinolytic, anti-inflammatory, and antithrombolytic pathways [4]. Defibrotide is approved for the treatment of adult and pediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction

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post-HCT in the United States [15] and Canada [16]. In the European Union, defibrotide is approved to treat severe hepatic VOD/SOS post-HCT in adults and pediatric patients age >1 month [16,17]. Before receiving approval from the US Food and Drug Administration in 2016, defibrotide was made available in the United States through an expanded-access study (ClinicalTrials.gov identifier NCT00628498; treatment investigative new drug [T-IND]), the largest prospective study of defibrotide in patients with VOD/SOS reported to date [18,19]. This T-IND study enrolled 1000 patients with confirmed VOD/SOS with or without MOD post-HCT; treatment with defibrotide resulted in a Kaplan-Meier–estimated Day 100 survival rate of 59% and a safety profile consistent with previous clinical studies [19]. Recently suggested clinical guidelines recommend early initiation of defibrotide following diagnosis by the EBMT criteria and continued administration for at least 21 days or until full resolution of VOD/SOS. In addition, defibrotide prophylaxis has demonstrated potential in clinical trials in high-risk pediatric and adult patients [20,21].

This post hoc analysis of post-HCT patients with VOD/SOS in the T-IND study examined the incidence of VOD/SOS in patients with bilirubin levels <2 mg/dL before and after Day 21 post-HCT and evaluated survival in adult and pediatric defibrotide-treated patients with or without hyperbilirubinemia and with or without MOD.

METHODS

*Study D*esign

The study design has been reported previously [18,19]. In brief, NCT00628498 was an open-label, single-arm, expanded-access study that provided defibrotide treatment to patients with hepatic VOD/SOS before US regulatory approval. Patients received 25 mg/kg/day defibrotide via i.v. infusion (given in 4 divided doses of 6.25 mg/kg every 6 hours) for a recommended duration of at least 21 days and until resolution of symptoms of VOD/SOS (and MOD if present).

The study protocol was approved by an independent Ethics Committee or Institutional Review Board at each site and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

*Eligibility C*riteria

The T-IND protocol originally required all patients to have a diagnosis of VOD/SOS by Day 35 post-HCT per the Baltimore criteria or biopsy and to have MOD by Day 45 post-HCT [19]. These criteria mirrored those of the phase 3 defibrotide study that was ongoing at the time of T-IND enrollment. When the phase 3 study concluded, the inclusion criteria for the T-IND were amended to allow for enrollment of patients diagnosed by the modified Seattle criteria, patients without MOD, or patients with onset of VOD/SOS after Day 35 [19]. The modified Seattle criteria used in this study required at least 2 of the following clinical findings: bilirubin ≥2 mg/dL, ascites (radiographic or physical examination), weight gain ≥5% above baseline, or hepatomegaly increased over baseline. MOD was defined as renal or pulmonary dysfunction by Day 45 post-HCT. Renal dysfunction was defined as serum creatinine three times or higher over the baseline value, a decrease in creatinine clearance

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or glomerular filtration rate to ≤40% of baseline, or dialysis dependence due to VOD/SOS. Pulmonary dysfunction was defined as oxygen saturation ≤90% on room air, a requirement for supplemental oxygen to maintain oxygen saturation >90%, or ventilator dependence not due to infection. Investigators reported the diagnostic criteria used for each patient. Patients with uncontrolled acute bleeding or hemodynamic instability and those receiving medications with a high risk of hemorrhagic complications were excluded [19].

Endpoints and Assessments

The primary efficacy endpoint was survival at Day 100 post-HCT. Safety endpoints included treatment-emergent and treatment-related adverse events (AEs) occurring up to 30 days after the last dose of defibrotide.

Statistical Analyses

This report presents the results of a post hoc analysis that included only those patients who were enrolled after the protocol amendment that permitted diagnosis of VOD/SOS using the modified Seattle criteria, when hyperbilirubinemia was no longer a requirement for diagnosis.

Exploratory post hoc analyses examined Day 100 survival post-HCT by the presence (icteric VOD/SOS) or absence (anicteric VOD/SOS) of hyperbilirubinemia at diagnosis and by the method of VOD/SOS diagnosis (Baltimore criteria versus modified Seattle criteria versus biopsy). The proportion of patients alive at Day 100 was estimated along with 95% confidence intervals (CIs). Baseline demographic and disease characteristics and the incidences of treatment-emergent AEs and serious AEs were summarized descriptively. Because this study was not powered for these post hoc analyses, no formal statistical comparisons were made. AEs of special interest included hemorrhage and hypotension.

RESULTS

Patient Demographics and Disease Characteristics

Of the 1000 post-HCT patients in the T-IND, 803 (80%) were enrolled after the protocol amendment, allowing diagnosis of VOD/SOS using the modified Seattle criteria, and were included in the post hoc analysis. The median age at HCT was 12 years (range, <1 to 77 years), and 203 of the 803 patients (25%) had a primary disease diagnosis of acute myelogenous leukemia (Table 1). The majority of patients (660 of 803; 82%) had received an allogeneic HCT, and 352 of 803 (44%) had VOD/SOS with MOD.

Of the 803 post-HCT patients in the study, 449 (56%) were diagnosed by the Baltimore criteria (which required hyperbilirubinemia), 331 (41%) were diagnosed by the modified Seattle criteria, and 23 (3%) were diagnosed by biopsy. MOD was reported in 226 of the 449 patients (50%) diagnosed by the Baltimore criteria, in 112 of the 331 (34%) diagnosed by the modified Seattle criteria, and in 14 of the 23 (61%) diagnosed by biopsy, respectively (Table 2).

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Incidence and Timing of Diagnosis of Anicteric VOD/SOS Post-HCT

Overall, 181 of the 803 patients (23%) had a bilirubin level <2 mg/dL at the diagnosis of VOD/SOS. In patients diagnosed using the modified Seattle criteria, 165 of 331 (50%) had a baseline bilirubin level <2 mg/dL at diagnosis (Table 3). Liver biopsies were performed in 23 patients to confirm the diagnosis of VOD/SOS; of those patients, 16 (70%) had a bilirubin level <2 mg/dL at diagnosis (Table 3). At diagnosis, 132 of 460 pediatric patients (29%) and 49 of 334 adult patients (15%) had a bilirubin level <2 mg/dL; 9 patients had missing data on bilirubin level at the time of diagnosis. Among the patients with bilirubin <2 mg/dL at diagnosis, 34 of 132 pediatric patients and 20 of 49 adult patients (41%) had MOD (Figure 1). Also in this subgroup of patients with bilirubin <2 mg/dL at diagnosis, VOD/SOS was diagnosed by Day 21 post-HCT in 106 of 132 pediatric patients (80%) and in 25 of 49 adult patients (51%; Figure 2).

Efficacy of Defibrotide in Anicteric versus Icteric VOD/SOS

In the overall post-HCT VOD/SOS group treated with defibrotide and enrolled after the protocol amendment allowing for diagnosis using the modified Seattle criteria (n = 803; including 9 patients without bilirubin measurement at diagnosis), estimated Day 100 survival was 62% (95% CI, 58% to 65%). Estimated Day 100 survival was 87% among patients with bilirubin <2 mg/dL and 54% among those with bilirubin ≥2 mg/dL (Figure 3A). In adults, estimated Day 100 survival was higher in patients with bilirubin <2 mg/dL compared with those with bilirubin ≥2 mg/dL; a similar trend was observed in pediatric patients. This pattern of response is also illustrated in the Kaplan-Meier–estimated survival curves shown in Figure 4. In both the adult and pediatric populations, Day 100 survival rates were higher in patients with MOD and bilirubin <2 mg/dL compared with patients without MOD with bilirubin ≥2 mg/dL (Figure 3B). Consistent with this observation, Day 100 survival was lowest in patients diagnosed by the Baltimore criteria regardless of MOD status (Figure 3C). Among patients with MOD, Day 100 survival was 47% (95% CI, 40% to 53%) in patients diagnosed by the Baltimore criteria, 62% (95% CI, 52% to 70%) in patients diagnosed by the modified Seattle criteria, and 71% (95% CI, 41% to 88%) in patients diagnosed by biopsy. Among those without MOD, the corresponding Day 100 survival was 62% (95% CI, 55% to 68%), 78% (95% CI, 71% to 83%), and 67% (95% CI, 28% to 88%), respectively.

Safety of Defibrotide in Anicteric versus Icteric VOD/SOS

Treatment-emergent AEs occurred in 565 of 803 (70%) of the total VOD/SOS post-HCT population. Both treatment-emergent AEs (61% versus 74%) and serious AEs (34% versus 58%) were lower in patients with a bilirubin level <2 mg/dL at diagnosis compared with those with bilirubin ≥2 mg/dL at diagnosis (Table 4). Treatment-emergent AEs and serious AEs tended to be lower in patients diagnosed with the modified Seattle criteria compared with those diagnosed using the Baltimore criteria (Table 5).

Treatment-emergent hypotension occurred in 87 of 803 patients (11%) in the total VOD/SOS post-HCT population; specifically, hypotension occurred in 79 of 613 patients (13%) with bilirubin ≥2 mg/dL and in 8 of 181 (4%) with bilirubin <2 mg/dL (Table 4). A total of 229 of the 803 patients (29%) experienced at least 1 hemorrhage, which was

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more common in patients with hyperbilirubinemia (191 of 613; 31%) than in those without hyperbilirubinemia (37 of 181; 20%).

DISCUSSION

In the T-IND, 181 of 803 patients (23%) had a bilirubin level <2 mg/dL at the diagnosis of VOD/SOS and would not have been diagnosed had the presence of hyperbilirubinemia been required (ie, the Baltimore criteria). This number includes 132 of 460 pediatric patients (29%) and 49 of 334 adult patients (15%) with a bilirubin level <2 mg/dL at the time of diagnosis. Notably, given the substantial proportion of patients in this analysis who were diagnosed using the Baltimore criteria, the 23% incidence of anicteric VOD/SOS may be an underestimate of the actual incidence in the clinical setting. In the population of patients diagnosed using the modified Seattle criteria, which does not require hyperbilirubinemia, 165 of 331 patients (50%) diagnosed with VOD/SOS had a bilirubin level <2 mg/dL at baseline. Importantly, a majority of patients (16 of 23; 70%) with biopsy-confirmed VOD/SOS did not present with hyperbilirubinemia.

Anicteric VOD/SOS was more common in pediatric patients than in adult patients but, importantly, was present in both groups. Nearly one half of the cases of anicteric VOD/SOS in adults occurred before Day 21 post-HCT, refuting the idea that anicteric VOD/SOS in adults occurs only after Day 21. Among both pediatric and adult patients, MOD was less common in those with anicteric VOD/SOS than in those with icteric VOD/SOS, suggesting that the presence of hyperbilirubinemia may represent a more advanced stage of the disease. Notably, we designated “anicteric” VOD/SOS based on the patient’s bilirubin level at the date of diagnosis; however, due to incomplete data at time points after diagnosis, no estimate of the proportion of patients with elevated bilirubin levels after the diagnosis date can be made.

Day 100 survival was lower in patients diagnosed with VOD/SOS with hyperbilirubinemia, and MOD was more common in these patients, both overall and by age group. This suggests that requiring hyperbilirubinemia for diagnosis may result in worse outcomes. The use of criteria that do not require hyperbilirubinemia for non–late-stage VOD/SOS, such as the modified Seattle or EBMT pediatric criteria, may allow for earlier identification and diagnosis.

The safety profile of defibrotide in the T-IND was similar to previous defibrotide studies. The idea that hyperbilirubinemia represents a more advanced stage of VOD/SOS is supported by data showing that the incidence of treatment-emergent AEs and serious AEs was lower in patients with bilirubin levels <2 mg/dL versus ≥2 mg/dL at diagnosis. In addition, the rates of treatment-emergent AEs and serious AEs tended to be lower in the patients diagnosis using the modified Seattle criteria compared with those diagnosed using the Baltimore criteria, suggesting more advanced disease in patients diagnosed with the Baltimore criteria.

There are some intrinsic limitations to this analysis. Because of its single-arm, open-label design, the analysis lacked an untreated control group. In addition, this expanded access

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study was not powered for statistical analyses within subgroups, and the available data were limited to those provided by the investigators. Given these limitations, a prospective study is needed to validate and expand on these results.

In conclusion, anicteric VOD/SOS occurred in both adult and pediatric patients post-HCT in this T-IND and was diagnosed both before and after Day 21 in both age groups. Survival in defibrotide-treated patients with a bilirubin level <2 mg/dL compared favorably with the overall study findings [19]. The lower Day 100 survival in patients diagnosed with a bilirubin level ≥2 mg/dL suggests that requiring hyperbilirubinemia may result in progression to a more advanced stage of disease, which is known to be associated with worse outcomes [22]. Collectively, these results highlight the need to maintain vigilance and awareness of the possibility of VOD/SOS at any time after HCT, even in the absence of elevated bilirubin levels, to facilitate earlier identification and intervention.

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Conflict of interest statement:

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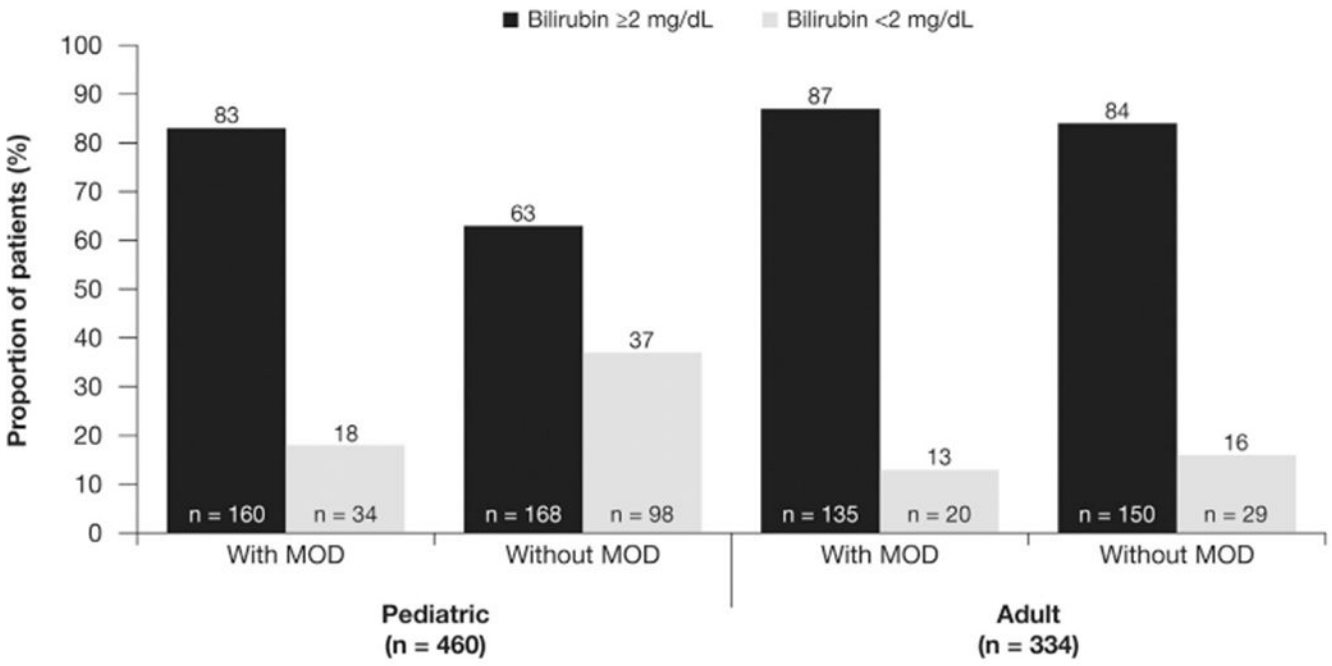

Figure 1.

Patients with VOD/SOS with and without MOD by bilirubin level and age group. Pediatric patients were age ≤16 years; adult patients were age >16 years.

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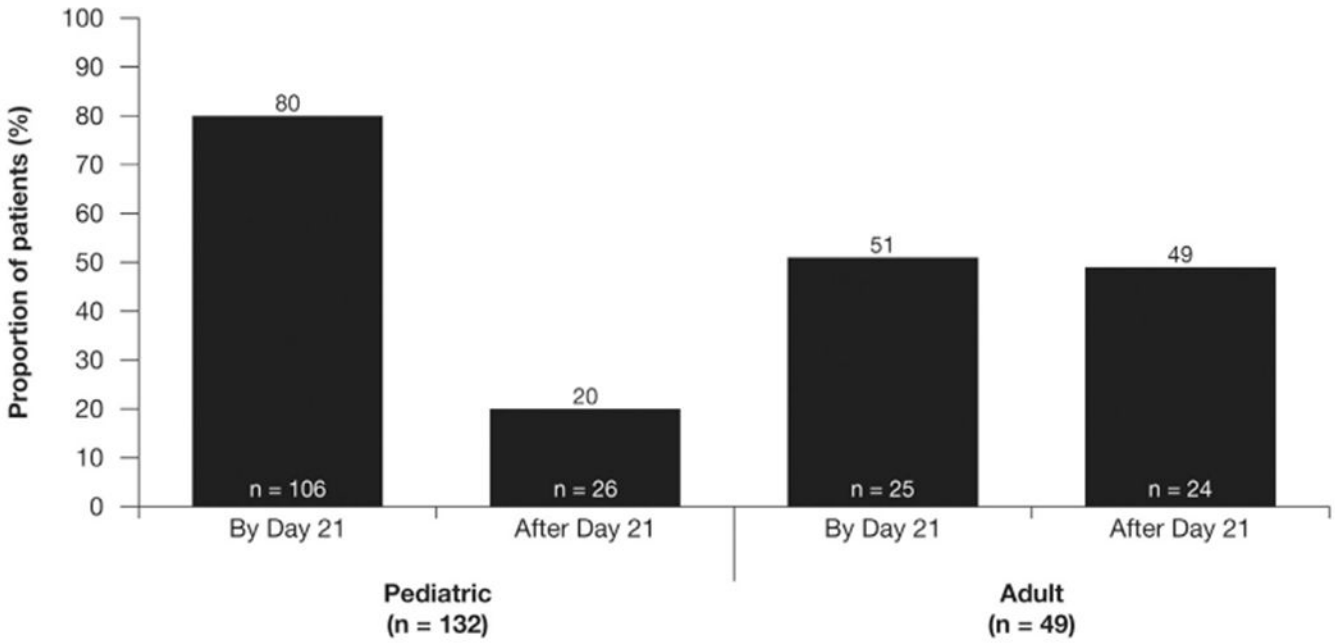

Figure 2.

Anicteric VOD/SOS (bilirubin <2 mg/dL) at time of diagnosis in pediatric and adult patients. Pediatric patients were age ≤16 years; adult patients were age >16 years.

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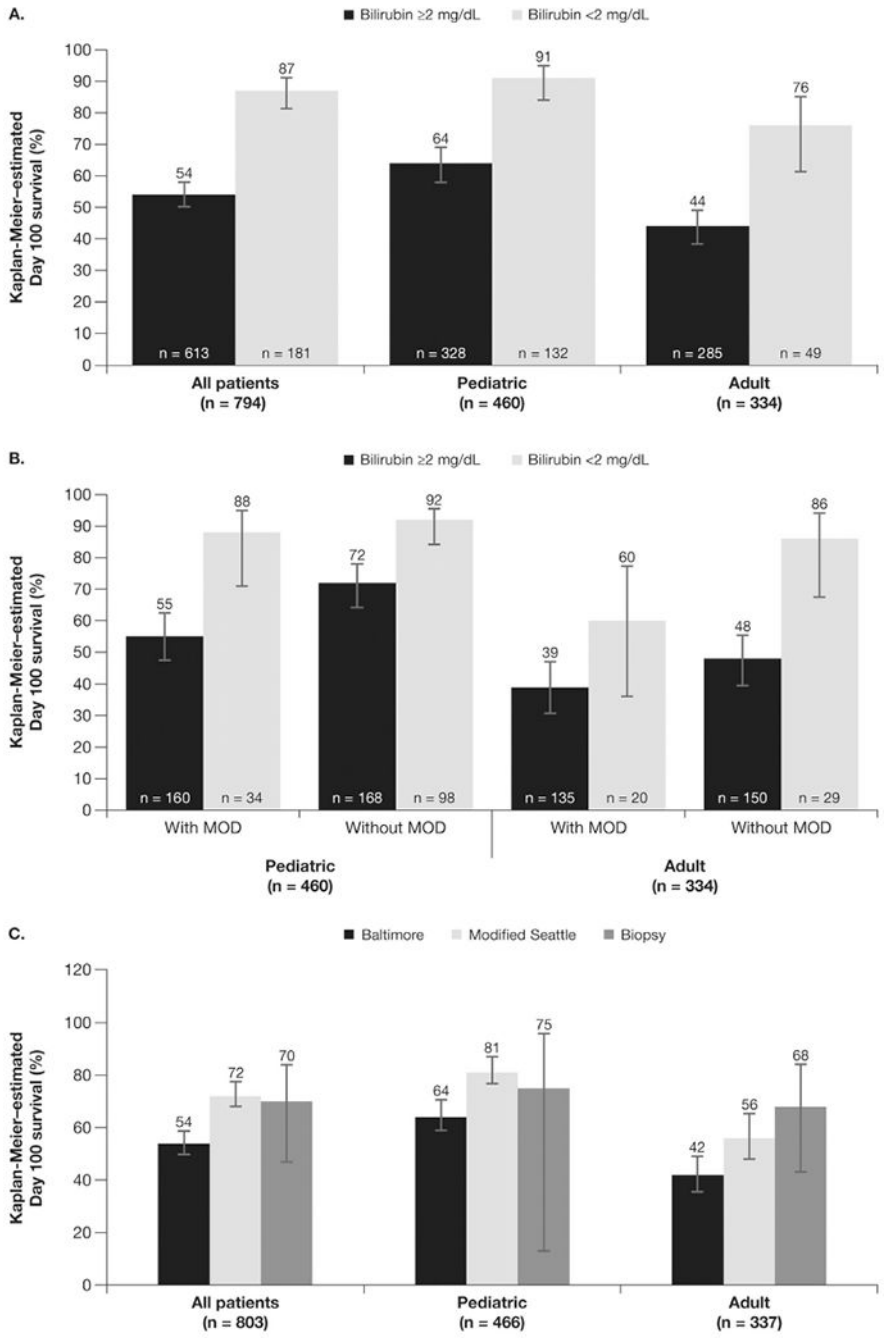

Figure 3.

Kaplan-Meier–estimated Day 100 survival in pediatric and adult patients by bilirubin level (A), presence of MOD (B), and criteria used for VOD/SOS diagnosis (C). Pediatric patients were age ≤16 years; adult patients were age >16 years. Error bars denote 95% CIs.

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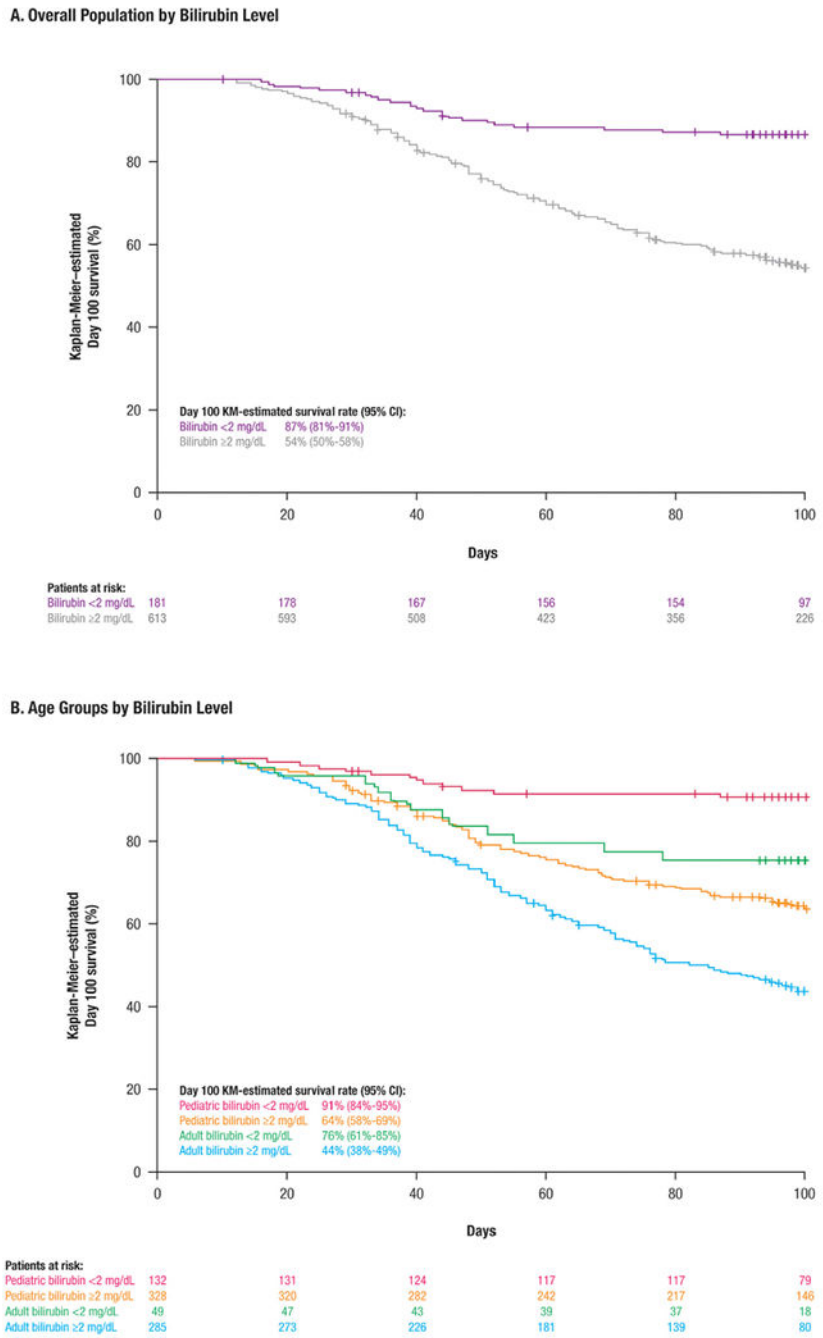

Figure 4.

Kaplan-Meier–estimated Day 100 survival curves by bilirubin level in the overall population (A) and by age (B). Pediatric patients were age ≤16 years; adult patients were age >16 years. Censored patients are represented with a + symbol.

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Table 1

Baseline Demographic and Disease Characteristics by Bilirubin Level at Diagnosis of VOD/SOS

		Bilirubin Level at Diagnosis of VOD/SOS*	
Characteristic	All VOD/SOS Post-HCT (N = 803)	<2 mg/dL (n = 181)	≥2 mg/dL (n = 613)
Age at HCT, yr, median (range)	12 (<1-77)	4 (<1-71)	15 (<1-77)
Age class at HCT, n (%)			
≤16 yr	466 (58)	132 (73)	328 (54)
>16 yr	337 (42)	49 (27)	285 (47)
Diagnostic criteria, n (%)			
Modified Seattle criteria†	331 (41)	165 (91)	158 (26)
Baltimore criteria	449 (56)	0	449 (73)
Biopsy†	23 (3)	16 (9)	6 (1)
Primary disease, n (%)			
Acute myelogenous leukemia	203 (25)	53 (29)	147 (24)
Acute lymphoblastic leukemia	152 (19)	17 (9)	134 (22)
Myelodysplastic syndrome	40 (5)	5 (3)	35 (6)
Neuroblastoma	101 (13)	51 (28)	48 (8)
Graft-versus-host disease prophylaxis, n (%)			
None	160 (20)	64 (35)	93 (15)
Tacrolimus	396 (49)	93 (51)	297 (49)
Methotrexate	263 (33)	49 (27)	209 (34)
Cyclosporine	209 (26)	14 (8)	195 (32)
Sirolimus	61 (8)	17 (9)	44 (7)
Other (not specified)	294 (37)	43 (24)	250 (41)
Type of HCT, n (%)			
Allogenous	660 (82)	122 (67)	531 (87)
Autogenous	141 (18)	59 (33)	80 (13)
Unknown	2 (<1)	0	2 (<1)
MOD present, n (%)	352 (44)	54 (30)	295 (48)

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[*] Of the 803 post-HCT patients in the T-IND, 9 had missing data on bilirubin level at diagnosis.

[†] Bilirubin data were missing for 8 patients diagnosed using the Seattle criteria and for 1 patient diagnosed by biopsy.

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Table 2

Baseline Demographic and Disease Characteristics by Diagnostic Criteria

		VOD/SOS Diagnosed by		
Characteristic	**All VOD/SOS Criteria (N = 803)**	**Baltimore Criteria (n = 449)**	**Modified Seattle Criteria (n = 331)**	**Biopsy (n = 23)**
Age at HCT, yr, median (range)	12 (<1-77)	14 (<1-77)	9 (<1-71)	43 (<1-68)
Age class at HCT, n (%)				
≤16 yr	466 (58)	251 (56)	211 (64)	4 (17)
>16 yr	337 (42)	198 (44)	120 (36)	19 (83)
Primary disease in >5% of all patients, n (%)				
Acute myelogenous leukemia	203 (25)	114 (25)	75 (23)	14 (61)
Acute lymphoblastic leukemia	152 (19)	95 (21)	56 (17)	1 (4)
Myelodysplastic syndrome	40 (5)	23 (5)	15 (5)	2 (9)
Neuroblastoma	101 (13)	42 (9)	59 (18)	0
Graft-versus-host disease prophylaxis, n (%)				
None	160 (20)	78 (17)	82 (25)	0
Tacrolimus	396 (49)	205 (46)	174 (53)	17 (74)
Methotrexate	263 (33)	130 (29)	121 (37)	12 (52)
Cyclosporine	209 (26)	145 (32)	64 (19)	0
Sirolimus	61 (8)	34 (8)	20 (6)	7 (30)
Other (not specified)	294 (37)	183 (41)	104 (31)	7 (30)
Type of HCT, n (%)				
Allogenic	660 (82)	379 (84)	259 (78)	22 (96)
Autogenous	141 (18)	69 (15)	71 (21)	1 (4)
Unknown	2 (<1)	1 (<1)	1 (<1)	0
MOD present, n (%)	352 (44)	226 (50)	112 (34)	14 (61)

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Table 3

VOD/SOS Diagnosis and Bilirubin Levels by Diagnostic Criteria

Diagnostic Criteria	Pediatric (n = 466)	Adult (n = 337)	All (N = 803)
Baltimore criteria, n (%)	251 (54)	198 (59)	449 (56)
Bilirubin ≥2 mg/dL	251 (100)	198 (100)	449 (100)
Seattle criteria, n (%)	211 (45)	120 (36)	331 (41)
Bilirubin <2 mg/dL	130 (62)	35 (29)	165 (50)
Bilirubin ≥2 mg/dL	76 (36)	82 (68)	158 (48)
Bilirubin missing	5 (2)	3 (3)	8 (2)
Biopsy criteria, n (%)	4 (<1)	19 (6)	23 (3)
Bilirubin <2 mg/dL	2 (50)	14 (74)	16 (70)
Bilirubin ≥2 mg/dL	1 (25)	5 (26)	6 (26)
Bilirubin missing	1 (25)	0	1 (4)

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Table 4

Summary of AEs

		Bilirubin Level at Diagnosis of VOD/SOS*	
n (%)	**All VOD/SOS Post-HCT (N = 803)**	**<2 mg/dL (n = 181)**	**≥2 mg/dL (n = 613)**
Treatment-emergent AEs	565 (70)	111 (61)	452 (74)
Serious AEs	421 (52)	62 (34)	357 (58)
AEs of interest			
Hemorrhage	229 (29)	37 (20)	191 (31)
Hypotension	87 (11)	8 (4)	79 (13)
Treatment-related AEs	167 (21)	34 (19)	132 (22)
Leading to discontinuation	100 (13)	20 (11)	79 (13)
Leading to death	23 (3)	5 (3)	18 (3)
Treatment-related AEs (>2%)†			
Pulmonary hemorrhage	35 (4)	7 (4)	28 (5)
Gastrointestinal hemorrhage	25 (3)	3 (2)	22 (4)
Epistaxis	18 (2)	3 (2)	15 (2)
Hemorrhage	7 (1)	3 (2)	4 (1)
Hypotension	11 (1)	1 (1)	10 (2)

*Of the 803 post-HCT patients in the T-IND, 9 patients had missing data on bilirubin level at diagnosis.

†Treatment-related AEs occurring in >2% of either bilirubin category.

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Table 5

AEs by Diagnostic Criteria

		VOD/SOS Diagnosed by:		
n (%)	**All VOD/SOS Criteria (N = 803)**	**Baltimore Criteria (n = 449)**	**Modified Seattle Criteria (n = 331)**	**Biopsy (n = 23)**
Treatment-emergent AEs	565 (70)	333 (74)	215 (65)	17 (74)
Most common (>5% in all patients)				
Multiorgan failure	87 (11)	62 (14)	23 (7)	2 (9)
Hypotension	86 (11)	55 (12)	28 (8)	3 (13)
Respiratory failure	67 (8)	38 (8)	27 (8)	2 (9)
Diarrhea	55 (7)	29 (6)	23 (7)	3 (13)
Veno-occlusive liver disease*	53 (7)	40 (9)	8 (2)	5 (22)
Pulmonary hemorrhage	51 (6)	34 (8)	17 (5)	0
Pyrexia	49 (6)	29 (6)	19 (6)	1 (4)
Vomiting	44 (5)	16 (4)	23 (7)	5 (22)
Renal failure	41 (5)	25 (6)	15 (5)	1 (4)
Serious AEs	421 (52)	273 (61)	135 (41)	13 (57)
Treatment-related AEs	167 (21)	90 (20)	74 (22)	3 (13)
Leading to discontinuation	100 (12)	58 (13)	41 (12)	1 (4)
Leading to death	23 (3)	16 (4)	7 (2)	0
Hemorrhage	229 (29)	139 (31)	83 (25)	7 (30)
Hypotension	87 (11)	56 (12)	28 (8)	3 (13)

*AEs were reported by investigators; by definition, all patients had veno-occlusive liver disease.

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