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Treatment Duration, Symptom Resolution, and Survival in Defibrotide-Treated Patients With Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome by Exposure to Inotuzumab Ozogamicin or Gemtuzumab Ozogamicin: Pooled Analysis of DEFIFrance and EBMT PASS Registries

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Background

- Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially fatal complication of hematopoietic cell transplantation (HCT) and has an associated mortality rate of >80% if left untreated[1,2]
- VOD/SOS occurs due to activation and damage of the sinusoidal endothelium[2,3]
- Inotuzumab ozogamicin (InO) and gemtuzumab ozogamicin (GO) are antibody-drug conjugates approved for CD22-positive B-cell acute lymphoblastic leukemia and CD33-positive acute myeloid leukemia, respectively[4]
  - However, both are considered unmodifiable high-risk factors for VOD/SOS based on the 2023 refined European Society for Blood and Marrow Transplantation (EBMT) classification criteria[4]
- Defibrotide (Defitelio®) has been shown to protect the endothelial cells and restore the thrombotic-fibrinolytic balance in vitro[5-7]
- Defibrotide is approved for treating severe VOD/SOS post-HCT in patients aged >1 month in the EU[6] and VOD/SOS with renal or pulmonary dysfunction post-HCT in the US[7]
- Clinical guidelines recommend prompt defibrotide initiation after the diagnosis of VOD/SOS[8,9]

Objective

- Report data from 2 real-world studies of defibrotide (DEFIFrance[10] and the EBMT Post-Authorization Safety Study [PASS][11]) to describe patient characteristics, treatment duration, VOD/SOS resolution, survival outcomes, and safety in a subpopulation of defibrotide-treated patients with or without exposure to InO/GO

Methods

- Data were pooled from the DEFIFrance and EBMT PASS registries to analyze a subpopulation of patients who were treated with defibrotide for VOD/SOS diagnosis and categorized by HCT status (post-HCT or non-HCT) and InO/GO exposure (InO/GO or non-InO/GO)
- DEFIFrance was an observational, post-marketing study to collect retrospective and prospective data on patients receiving defibrotide at 53 French transplant centers from July 2014 to March 2020[10]
  - The primary endpoints were Kaplan-Meier (KM)–estimated day 100 survival post-HCT and complete response of VOD/SOS at day 100
  - The secondary endpoint included the incidence of adverse events of interest
- EBMT PASS was a multinational, prospective, observational study that enrolled patients treated with defibrotide from April 2015 to July 2018[11]
  - The primary endpoint was incidence of serious adverse events of interest in patients with severe VOD/SOS up to 12 months post-HCT
  - The secondary endpoints included day 100 survival post-HCT and overall rate of VOD/SOS resolution
- Diagnosis of VOD/SOS was based on investigator discretion using classic/standard criteria (including, but not limited to, hyperbilirubinemia, hepatomegaly, ascites, and weight gain >5%)

Results

Table 1. Patient Demographic and Clinical Characteristics

	Post-HCT VOD/SOS			Non-HCT VOD/SOS		
	InO/GO n=38	Non-InO/GO n=376	Overall N=414	InO/GO n=17	Non-InO/GO n=31	Overall N=48
Median age (range), years	42 (1-67)	35 (0-74)	37 (0-74)	57 (7-72)	10 (2-71)	37 (2-72)
Sex, n (%)						
Male	19 (50)	226 (60)	245 (59)	7 (41)	20 (65)	27 (56)
Previous treatment with GO, n (%)						
No	7 (18)	376 (100)	383 (93)	4 (24)	31 (100)	35 (73)
Yes	31 (82)	0	31 (7)	13 (76)	0	13 (27)
Previous treatment with InO, n (%)						
No	26 (68)	303 (81)	329 (79)	13 (76)	31 (100)	44 (92)
Yes	7 (18)	0	7 (2)	4 (24)	0	4 (8)
Missing	5 (13)	73 (19)	78 (19)	0	0	0
Conditioning (MAC only), n (%)	17 (45)	237 (63)	254 (61)	-	-	-
Number of previous HCTs, n (%)						
1	8 (21)	90 (24)	98 (24)	-	-	-
2+	0	17 (5)	17 (4)	-	-	-
Missing	30 (79)	269 (72)	299 (72)	-	-	-
Type of transplant,[a] n (%)						
Autograft	1 (3)	59 (16)	60 (15)	-	-	-
Allograft	37 (97)	316 (84)	353 (85)	-	-	-

Percentages have been rounded, and therefore may not precisely sum to 100%.
[a]Type of transplant for 1 patient (who did not achieve a CR) in the non-InO/GO subpopulation was missing.
CR, complete resolution; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; InO, inotuzumab ozogamicin; MAC, myeloablative conditioning; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

- Analysis included 462 patients treated with defibrotide for post-HCT (n=414) and non-HCT VOD/SOS (n=48)
  - Of these, 55 were previously treated with InO/GO (12%; InO: n=11, GO: n=44)
- Acute myeloid leukemia was the most common primary disease in patients across both DEFIFrance and EBMT PASS registries, although precursor lymphoid neoplasm was equally common in the EBMT PASS registry

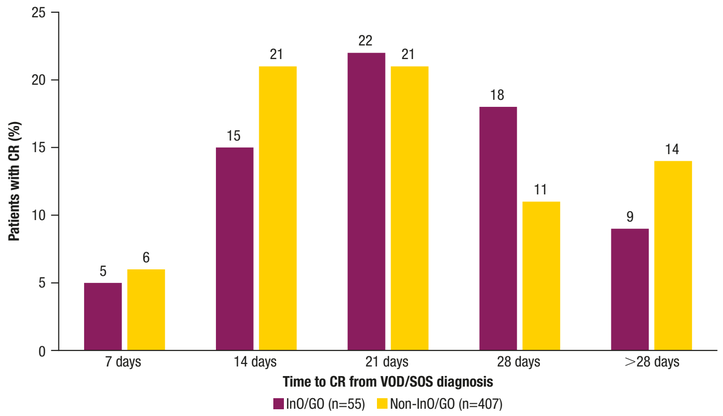
Table 2. Treatment Duration, Complete Response Rates, and Time From VOD Diagnosis to Resolution by HCT Status and InO/GO Exposure

	Post-HCT VOD/SOS		Non-HCT VOD/SOS	
	InO/GO n=38	Non-InO/GO n=376	InO/GO n=17	Non-InO/GO n=31
Median (IQR) days of defibrotide treatment	18 (10, 22)	16 (11, 22)[a]	16 (10, 22)	10 (7, 15)
Patients with resolution, n (%)	29 (76)	272 (72)	9 (53)	20 (65)
Median (IQR) days from VOD diagnosis to resolution[b]	20 (14, 25)	19 (12, 25)	21 (12, 24)	11 (9, 16)

[a]n=375; duration of defibrotide treatment for 1 patient in the non-InO/GO subpopulation was missing. [b]For patients with resolution.
CR, complete resolution; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; InO, inotuzumab ozogamicin; IQR, interquartile range; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

- Overall, median time from VOD diagnosis to defibrotide initiation was 0 days (interquartile range [IQR]: 0, 1)
- The median treatment duration for non-InO/GO patients (n=407) was numerically shorter than for InO/GO patients (n=55) (15 days [IQR: 10, 22] vs 18 days [IQR: 10, 22])

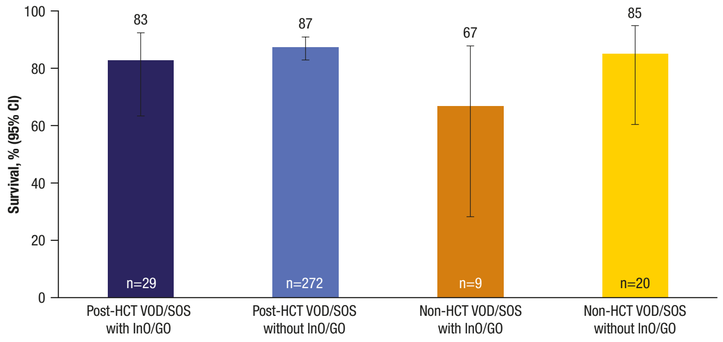
Figure 1. Time to VOD/SOS Resolution and Percentage of Patients With VOD/SOS Resolution by InO/GO Exposure



CR, complete resolution; GO, gemtuzumab ozogamicin; InO, inotuzumab ozogamicin; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

- VOD/SOS resolution occurred in 38/55 (69%) of InO/GO patients and 292/407 (72%) of non-InO/GO patients, with a median time to resolution of 20 days (IQR: 13, 25) and 18 days (IQR: 12, 24), respectively

Figure 2. KM-Estimated Day 100 Survival in Patients With CR by HCT Status and InO/GO Exposure[a]



[a]Day 100 post-HCT for HCT patients and day 100 after starting defibrotide for non-HCT patients.
CI, confidence interval; CR, complete resolution; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; InO, inotuzumab ozogamicin; KM, Kaplan-Meier.

- KM-estimated survival at day 100 post-HCT was 83% (95% confidence interval [CI]: 63%, 92%) in patients with InO/GO and 87% (95% CI: 83%, 91%) in those without InO/GO
- KM-estimated survival at day 100 since starting defibrotide treatment in non-HCT patients was 67% (95% CI: 28%, 88%) in patients with InO/GO exposure and 85% (95% CI: 60%, 95%) in those without InO/GO exposure

Table 3. Serious TEAEs of Interest by InO/GO Status for All Post-HCT and Non-HCT Patients

Serious TEAEs of Interest	InO/GO n=55	Non-InO/GO n=407	Overall N=462
Any serious TEAE of interest, n (%)	15 (27)	107 (26)	122 (26)
Serious TEAEs of interest by category, n (%)			
Infection	9 (16)	57 (14)	66 (14)
Hemorrhage	10 (18)	50 (12)	60 (13)
Bleeding	0	8 (2)	8 (2)
Hypotension	0	8 (2)	8 (2)
Coagulopathy	1 (2)	4 (1)	5 (1)
Embolism	0	2 (0.5)	2 (0.4)
Septicemia	0	2 (0.5)	2 (0.4)
Thromboembolic events	0	2 (0.5)	2 (0.4)
Thrombosis	0	2 (0.5)	2 (0.4)
Serious TEAEs of interest in ⩾2% of patients in either group, n (%)			
Infection	2 (4)	11 (3)	13 (3)
Cytomegalovirus infection	0	8 (2)	8 (2)
Cytomegalovirus infection reactivation	3 (6)	4 (1)	7 (2)
Enterococcal infection	2 (4)	2 (0.5)	4 (1)
Hemorrhage	4 (7)	8 (2)	12 (3)
Cystitis hemorrhagic	0	11 (3)	11 (2)
Gastrointestinal hemorrhage	2 (4)	6 (2)	8 (2)
Viral hemorrhagic cystitis	3 (5)	5 (1)	8 (2)

GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; InO, inotuzumab ozogamicin; TEAE, treatment-emergent adverse event.

- Serious treatment-emergent adverse events (TEAEs) of interest occurred in 27% of InO/GO patients and 26% of non-InO/GO patients
- The most common serious TEAEs of interest were infection (16% and 14%) and hemorrhage (18% and 12%), respectively

Conclusions

- Exposure to InO/GO was common among patients treated with defibrotide in the DEFIFrance and EBMT PASS registries, consistent with being a recognized risk factor for VOD/SOS[4]
- The VOD/SOS resolution rate and time to resolution and defibrotide treatment duration appear similar regardless of InO/GO exposure
- The safety profile of defibrotide in this pooled analysis is consistent with pivotal trial results regardless of InO/GO exposure[12-14]
- These findings highlight the importance of vigilant monitoring, prompt VOD diagnosis and defibrotide treatment with therapies that may increase the risk of VOD
- This analysis is limited by the lack of matching between the InO/GO and the non-InO/GO groups and the comparison could be confounded by other factors

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