PO-203

Defibrotide treatment for veno-occlusive disease/sinusoidal obstruction syndrome after haematopoietic cell transplantation: outcomes by severity and multiorgan failure status in an observational registry study

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Background

- Severe hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of haematopoietic cell transplantation (HCT)[1]
  - The most severe form of VOD/SOS is associated with multiorgan dysfunction/failure (MOD/MOF) and a mortality rate of >80% if treated with supportive care alone[1]
- Response to VOD/SOS treatment may be more favourable if treatment is initiated early (prior to MOD/MOF)[2]
- Clinical studies of defibrotide have demonstrated safety and efficacy in patients with VOD/SOS post-HCT, including those with severe VOD/SOS[3–6]
- Defibrotide is approved for the treatment of severe hepatic VOD/SOS post-HCT in adult and paediatric patients aged >1 month in the European Union[7]
- As a specific obligation of conditional approval, a disease registry was established to collect real-world safety data in the post-approval setting in Europe

Objective

- This exploratory subgroup analysis evaluated outcomes in patients who received defibrotide for the treatment of VOD/SOS post-HCT, including those with non-severe VOD/SOS and those with severe VOD/SOS, including MOD/MOF

Methods

- This multicentre, international, prospective, observational study (ClinicalTrials.gov Identifier: NCT03032016), performed by the EBMT, enrolled patients treated with defibrotide in EBMT-member transplantation centres from April 2015 to July 2018
  - Investigators diagnosed VOD/SOS using classical/standard criteria (including but not limited to hyperbilirubinaemia, hepatomegaly, ascites, and weight gain >5%)
  - Severity grading criteria were not predefined in the protocol; investigators graded VOD/SOS severity based on typical clinical practice
  - Patients with renal, pulmonary, or cerebral dysfunction/failure, as judged by the investigator, were diagnosed with MOD/MOF
  - There were no specific exclusion criteria; however, treating physicians were alerted to contraindications, special warnings, and precautions detailed in the defibrotide summary of product characteristics
- Patient information was collected at baseline, 100 days, 6 months, and 12 months post-HCT
  - The primary study endpoint was the incidence of serious adverse events of interest up to 12 months post-HCT in patients with severe VOD/SOS
  - Secondary endpoints included Day 100 survival and overall rate of VOD/SOS (and MOD/MOF, if present) resolution (as defined by the investigator) up to 12 months post-HCT
- Summary statistics were calculated for baseline data and safety variables; outcome analyses are descriptive

Results

Table 1. Baseline demographics and clinical characteristics.

Characteristic	Non-severe VOD/SOS post-HCT (N=42)	Severe VOD/SOS post-HCT: No MOD/MOF (N=26)	Severe VOD/SOS post-HCT: With MOD/MOF (N=36)
Median (range) age at HCT, years	13.1 (0, 69)	11.7 (1, 65)	21.1 (0, 68)
<18 years, n (%)	25 (60)	17 (65)	17 (47)
Primary disease in >10% of patients, n (%)			
AML[a]	6 (14)	7 (27)	7 (19)
Precursor lymphoid neoplasms	9 (21)	1 (4)	13 (36)
MDS/myeloproliferative disease[b]	11 (26)	8 (31)	4 (11)
Solid tumour[c]	6 (14)	5 (19)	2 (6)
Allogeneic HCT, n (%)	35 (83)	21 (81)	34 (94)
Myeloablative conditioning regimen[d]	27 (77)	19 (91)	28 (82)
Median (IQR) defibrotide exposure, days	15.5 (13.0, 21.0)	19.5 (11.0, 27.0)	15.0 (10.0, 24.0)

VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, haematopoietic cell transplantation; MOD/MOF, multiorgan dysfunction/failure; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; IQR, interquartile range.
[a]Includes related precursor neoplasms, including AML with maturation (FAB M2).
[b]Includes myeloproliferative neoplasia and MDS resulting in acute leukaemia.
[c]Excludes breast cancer.
[d]Denominator is the number of patients with allogeneic HCT.

Table 2. SAEs of interest.

	Non-severe VOD/SOS post-HCT (N=42)	Severe VOD/SOS post-HCT: No MOD/MOF (N=26)	Severe VOD/SOS post-HCT: With MOD/MOF (N=36)
SAEs of interest, n (%)[a,b]	9 (21)	7 (27)	13 (36)
SAEs of interest by category, n (%)[c]			
Infection	6 (14)	5 (19)	10 (28)
Bleeding	4 (10)	2 (8)	6 (17)
Hypotension	0	1 (4)	0
Thromboembolic events	1 (2)	1 (4)	0
Most common (≥5%) individual SAEs of interest, n (%)			
Gastrointestinal bleeding	2 (5)	1 (4)	3 (8)
Pneumonia	0	2 (8)	3 (8)
Sepsis	0	3 (12)	2 (6)
Urinary tract bleeding	0	1[d] (4)	2 (6)

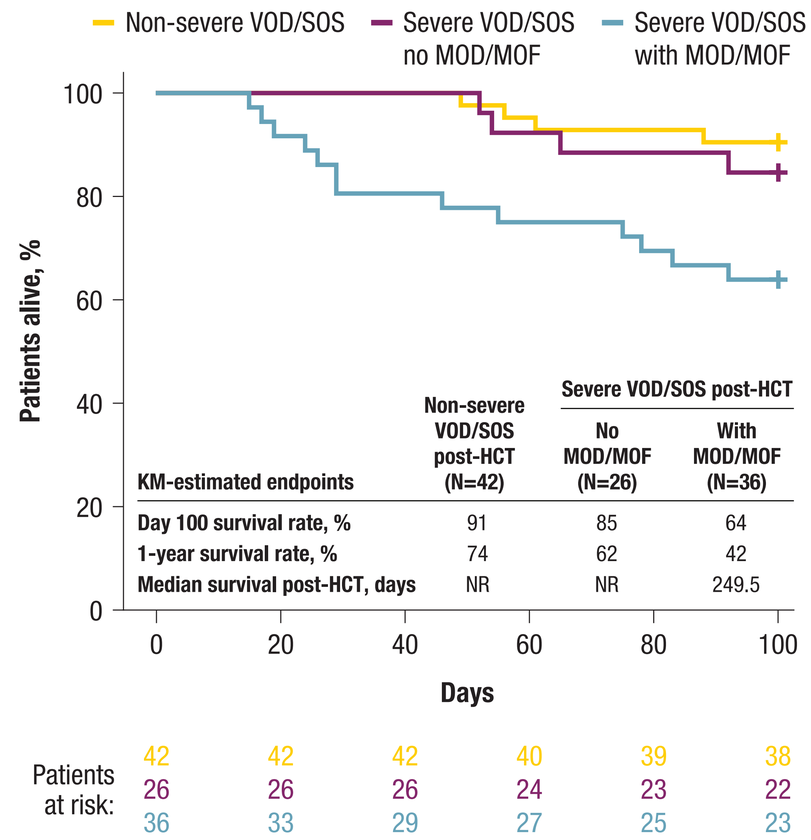
SAE, serious adverse event; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, haematopoietic cell transplantation; MOD/MOF, multiorgan dysfunction/failure.
[a]Values indicate the number of patients who had ≥1 SAE of interest in a given category; patients may have had multiple events within that category.
[b]SAEs of interest included haemorrhage, hypotension, coagulopathy, allergic/hypersensitivity reactions, injection-site reactions, infection/septicaemia, and thromboembolic events.
[c]There were no events reported for the other defined SAEs of interest.
[d]Recorded as "bleeding, other: urinary."

Table 3. Deaths due to VOD/SOS.

	Non-severe VOD/SOS post-HCT (N=42)	Severe VOD/SOS post-HCT: No MOD/MOF (N=26)	Severe VOD/SOS post-HCT: With MOD/MOF (N=36)
Deaths, n (%)	11 (26)	10 (38)	21 (58)
Due to VOD/SOS[a]	0	2 (20)	11 (52)

VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; HCT, haematopoietic cell transplantation; MOD/MOF, multiorgan dysfunction/failure.
[a]Denominator is the number of deaths.

Figure 1. KM-estimated survival.



KM-estimated endpoints	Non-severe VOD/SOS post-HCT (N=42)	Severe VOD/SOS post-HCT: No MOD/MOF (N=26)	Severe VOD/SOS post-HCT: With MOD/MOF (N=36)
Day 100 survival rate, %	91	85	64
1-year survival rate, %	74	62	42
Median survival post-HCT, days	NR	NR	249.5

KM, Kaplan-Meier; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; MOD/MOF, multiorgan dysfunction/failure; HCT, haematopoietic cell transplantation; NR, not reached.

VOD/SOS resolution

- At 1 year, VOD/SOS symptoms had resolved in 40 (95%) patients with non-severe VOD/SOS; among patients with severe VOD/SOS, symptoms had resolved in 24 (92%) and 23 (64%) patients with no MOD/MOF and with MOD/MOF, respectively
  - The cumulative rate of VOD/SOS resolution at Day 100, with death as a competing event, was 95% in non-severe VOD/SOS, 88% in severe VOD/SOS with no MOD/MOF, and 61% in severe VOD/SOS with MOD/MOF

Conclusions

- Rates of Day 100 survival and VOD/SOS resolution were consistent with a previous report of defibrotide in the post-approval setting,[8] with better outcomes observed in patients with less severe forms of the disease
- The safety profile of defibrotide was consistent with previous reports[3–6]
- Real-world data provide valuable validation of the results from clinical studies
- Study limitations include potential differences in the way VOD/SOS was diagnosed and disease severity was graded due to the absence of protocol-specified definitions, in addition to the limitations inherent to a registry study

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