ELSEVIER

Blood 142 (2023) 7204–7205

The 65th ASH Annual Meeting Abstracts

**ONLINE PUBLICATION ONLY**

## 901.HEALTH SERVICES AND QUALITY IMPROVEMENT - NON-MALIGNANT CONDITIONS

### Systematic Literature Review of Incidence and Management of Non-HCT-Related Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS)

*Lin Fan[1], Fiona Stewart[2], Kimberly Ruiz[2], Malia Gill[2], Darsh Devani[2], Nicole Fusco[2], Wayne Su[1], Vian Amber[3], Alexandra Gangi[4], Raj Hanvesakul[3]*

[1] Jazz Pharmaceuticals, Philadelphia, PA
[2] Xcenda LLC, Conshohocken, PA
[3] Jazz Pharmaceuticals, Oxford, United Kingdom
[4] Cedars-Sinai Medical Center, Los Angeles, CA

**Background:** VOD/SOS is a potentially life-threatening complication caused by damage to sinusoidal endothelial cells. It has historically been associated with toxicity from conditioning regimens preceding hematopoietic cell transplantation (HCT), but its epidemiology and characteristics outside the HCT setting are not well understood. We conducted a systematic review to examine the incidence, mortality, diagnosis, and the burden of illness of non-HCT VOD/SOS.

**Methods:** We searchedMEDLINE and Embase (2002-2023), as well as recent congress proceedings (2019-2023) for studies reporting the following in the non-HCT VOD/SOS setting: incidence, diagnosis, relevant medical history, disease management, clinical burden, health-related quality of life, costs, and patients' (pts) unmet needs. All study designs were eligible except case series with <5 participants. Studies of pulmonary VOD or VOD/SOS resulting from ingestion of pyrrolizidine alkaloids were excluded. Two independent reviewers screened titles/abstracts and full-text articles and assessed the methodological quality of studies.

**Results:** Of 3874 records screened, 92 studies were included; 57% were retrospective cohort studies and 70% were conducted in the United States or Europe. VOD/SOS was reported in 17 acute myeloid leukemia (AML) studies and 13 acute lymphoblastic leukemia (ALL) studies. The highest incidences of non-HCT VOD/SOS occurred in pts with colorectal liver metastases (CLM; median 35%) and Wilms tumor (median 14%; **Table 1**). The occurrences of severe non-HCT VOD/SOS and mortality are provided in **Table 2**.

Clinical criteria (eg, McDonald, Seattle, or Baltimore) were widely used to diagnose both hematological (i.e., AML and ALL) and nonhematological disease (i.e., Wilms tumor), while Rubbia-Brandt histological criteria were used to diagnose VOD/SOS in pts with CLM.

While most studies did not report how non-HCT VOD/SOS was managed, 26 studies reported defibrotide use: 80/112 pts (71%) with hematologic cancer and 223/309 pts (72%) in other disease settings. In 7/26 studies, all pts who received defibrotide recovered. Two of 26 studies reported high rates of recovery from VOD/SOS at 70 days following defibrotide initiation: one with 71% of patients alive at day 70 following the start of defibrotide (58/82 pts) and one with 83% of patients alive at day 70 (5/6 pts). Nine studies did not report any outcomes related to defibrotide and another did not distinguish between outcomes in pts treated with defibrotide compared with other treatments. No defibrotide use was reported in studies evaluating pts with CLM.

Among non-defibrotide treatments, the most reported VOD/SOS treatment was supportive therapy (14%; 13/92 studies), followed by switching or pausing chemotherapy (11%; 10/92 studies). One study reported outcomes for 206 children who received supportive care for VOD/SOS during 6-thioguanine therapy for ALL; only three pts had acute hepatic failure and all pts recovered from VOD/SOS. Of the studies reporting switching or pausing chemotherapy to manage VOD/SOS, four studies reported 100% recovery from VOD/SOS, and five studies did not report treatment outcomes. The severity of VOD/SOS in these pts was unknown.

Four studies reported any adverse events (AEs) in pts treated for VOD/SOS: two reported zero AEs (in four children with ALL treated with defibrotide and two children with Wilms tumor treated with N-acetylcsteine); one reported AEs in 27% (of 82 defibrotide-treated pts, mostly with hematologic cancers); and one reported ≥1 treatment-emergent serious AE of interest in 15% (of 46 pts with hematologic or nonhematologic cancers treated with defibrotide), including infection (9%) and hemorrhage (9%).

**Conclusions:** Non-HCT VOD/SOS occurs in diverse disease areas, including hematologic and solid tumor cancers. A lack of consensus regarding VOD/SOS diagnosis in the non-HCT setting may lead to underdiagnosis; therefore, clinicians should be vigilant for VOD/SOS even in non-HCT pts. Though defibrotide is approved for post-HCT VOD/SOS, there is no approved therapy for non-HCT VOD/SOS; future trials should focus on diagnosis and treatment outside the HCT setting, which represents a significant unmet need. Limitations include a lack of population-based studies to estimate true incidence and that the evidence is based on studies whose main objective was not to investigate non-HCT VOD/SOS.

**Disclosures Fan:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Stewart:** *Jazz Pharmaceuticals:* Consultancy. **Ruiz:** *Jazz Pharmaceuticals:* Consultancy. **Gill:** *Jazz Pharmaceuticals:* Consultancy. **Devani:** *Jazz Pharmaceuticals:* Consultancy. **Fusco:** *Jazz Pharmaceuticals:* Consultancy. **Su:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Amber:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Hanvesakul:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company.

**OffLabel Disclosure:** Defibrotide is approved for the treatment of severe VOD/SOS post-HCT in patients aged >1 month in the European Union and for VOD/SOS with renal or pulmonary dysfunction post-HCT in the United States.

**Table 1. Non-HCT VOD/SOS Occurrence**

| Disease | Therapy during/prior to VOD/SOS onset | Incidence, median % (range) | Number of studies |
|---|---|---|---|
| CLM | OBC | 35% (11%-58%) | 9 |
| Wilms tumor | Vincristine and actinomycin D | 14% (11%-45%) | 6 |
| Transfusion-dependent beta thalassemia | Beti-cel | 11% (-) | 1 |
| AML | GO | 5% (1%-33%) | 17 |
| ALL | 6-TG | 7% (0%-23%) | 7 |
| ALL | INO | 3% (2%-15%) | 5 |
| ALL | PEG | 3% (-) | 1 |
| Liver transplant for various indications | - | 3% (0%-14%) | 10 |

6-TG, 6-thioguanine; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLM, colorectal liver metastases; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; INO, inotuzumab ozogamicin; OBC, oxaliplatin-based chemotherapy; PEG, pegylated asparaginase; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

-, no data available.

**Table 2. Severity and Mortality in Non-HCT VOD/SOS**

| Initial disease setting (before/during VOD/SOS onset) | Median % (range) with severe VOD/SOS and/or MOF (as a proportion of non-HCT VOD/SOS cases) | Median % (range) of deaths attributed to non-HCT VOD/SOS (as a proportion of non-HCT VOD/SOS cases) | Number of studies |
|---|---|---|---|
| ALL | 15% (10%-20%) | 3.0% (0%-67%) | 7 |
| AML | 38% (33%-43%) | 31.4% (0%-100%) | 8 |
| Colorectal liver metastases | 11%[a] (0%-35.4%) | 0% (0%-0%) | 1 |
| Various indications for liver transplant | 14% (-) | 7.3% (0%-29%) | 5 |
| Studies including >1 hematologic cancer | 28% (-) | 48% (-) | 1 |
| Studies including >1 nonhematologic cancer | 38%[b] (31%-70%) | 14% (0%-25%) | 3 |
| Wilms tumor | 71.4% (40%-100%) | 0% | 1 |
| Liver cancer | - | - | - |
| Transfusion-dependent beta-thalassemia | - | - | - |
| Studies including >1 cancer (type of cancer not reported) | 40% (-) | 13.6% (0%-25.6%) | 3 |

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; MOF, multiorgan failure; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

-, no data available.

**Figure 1**

https://doi.org/10.1182/blood-2023-181696