P1303

Impact of Conditioning Intensity on Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome Severity and Outcomes in Adult Hematopoietic Cell Transplant Patients: Results From the DEFIFrance Registry

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Background

- Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening 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] and is likely associated with conditioning regimens preceding HCT[4]
- Myeloablative conditioning (MAC) regimens are widely used for patients with hematologic malignancies undergoing autologous and allogeneic HCT, but reduced-intensity conditioning (RIC) regimens have made HCT available for patients with preexisting comorbidities or those unfit to tolerate MAC[5]
- While RIC regimens are thought to decrease the likelihood of VOD/SOS over MAC regimens, this complication does still occur following RIC and can be severe[6,7]
- Defibrotide (Defitelio®) is approved in the European Union for the treatment of severe hepatic VOD/SOS post-HCT in patients aged >1 month.[8] In the United States, defibrotide is approved for the treatment of VOD/SOS in patients with renal or pulmonary dysfunction post-HCT[9]
- Clinical guidelines recommend prompt defibrotide initiation after the diagnosis of VOD/SOS[10,11]
- Defibrotide has been shown to protect the endothelial cells and restore the thrombotic-fibrinolytic balance in vitro[12]
- 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[13]

Objective

- Describe VOD/SOS severity, clinical outcomes, and survival in adult patients who received RIC or MAC regimens followed by defibrotide for the treatment of VOD/SOS after HCT in the DEFIFrance registry

Methods

- Investigators diagnosed VOD/SOS using classical/standard criteria (including but not limited to hyperbilirubinemia, hepatomegaly, ascites, and weight gain >5%)
- In DEFIFrance,[13] VOD/SOS severity was categorized using adult European Society for Blood and Marrow Transplantation (EBMT) criteria for patients aged ⩾18 years
- The primary endpoints were Kaplan-Meier (KM)–estimated day 100 survival and complete response (CR; total serum bilirubin <2 mg/dL and multiorgan failure resolution per investigators' assessment) post-HCT of VOD/SOS at day 100
- A secondary endpoint was incidence of serious treatment-emergent adverse events of special interest (including hemorrhages, coagulopathies, infections, and thromboembolic events)

Results

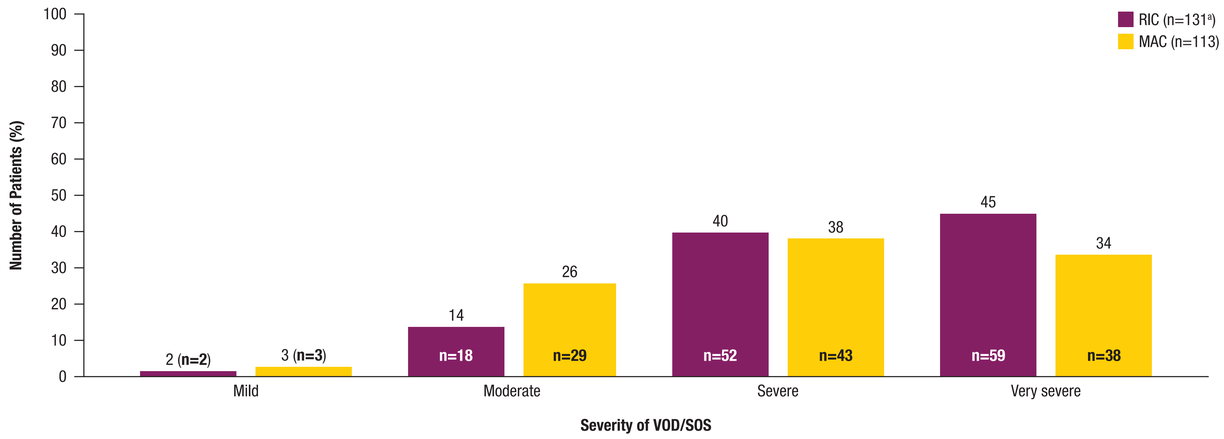
Table 1. Baseline Patient Demographic and Clinical Characteristics

	Patients Receiving RIC (n=134)	Patients Receiving MAC (n=113)
Median age (range), years	56 (18-74)	47 (18-68)
Male, n (%)	75 (56)	75 (66)
Primary disease, n (%)		
AML	48 (36)	32 (28)
MDS	28 (21)	11 (10)
Lymphoma	18 (13)	32 (28)
ALL	15 (11)	26 (23)
Myelofibrosis	15 (11)	4 (4)
AL mixed phenotype	1 (1)	0 (0)
Other	9 (7)	8 (7)
Number of previous HCTs,[a] n (%)		
0	110 (83)	103 (91)
1	20 (15)	6 (5)
2	2 (1)	4 (4)
3	1 (1)	0
Allogeneic HCT Donor type, n/N (%)	132/134 (99)	93/113 (82)
Non-parent (unrelated)	61/132 (46)	41/93 (44)
HLA similar to siblings	38/132 (29)	33/93 (35)
Haplo-identical	32/132 (24)	16/93 (17)
Umbilical cord blood cells	1/132 (1)	3/93 (3)

[a]Number of prior HCT treatments was missing for 1 patient receiving RIC and was excluded from percentage calculations.
AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; RIC, reduced-intensity conditioning.

- The median (interquartile range [IQR]) time from HCT to VOD/SOS diagnosis was shorter in the RIC subgroup (12 [6, 21] days) vs the MAC subgroup (14 [9, 26] days)
- The median (IQR) duration of defibrotide treatment was similar for both subgroups (RIC: 15 [10, 22] days; MAC: 16 [12, 22] days)

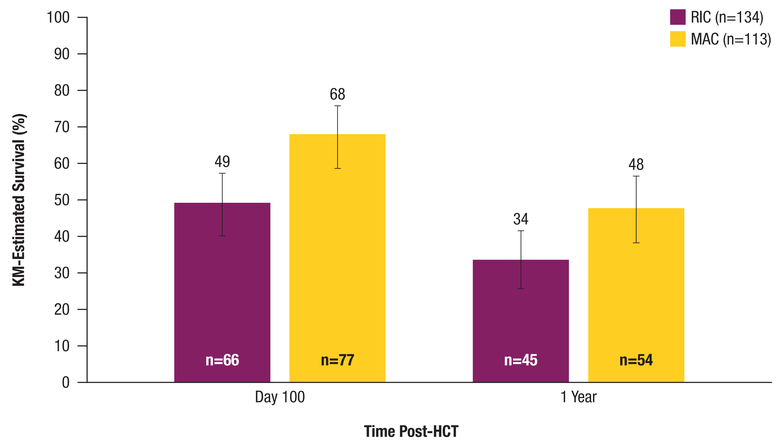
Figure 1. Severity of VOD/SOS for Patients Treated With RIC or MAC



[a]VOD/SOS severity was missing for 3 patients receiving RIC and were excluded from percentage calculations.
MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

- A higher proportion of very severe VOD/SOS was noted in patients receiving RIC (45%) vs MAC (34%), with a corresponding lower proportion of moderate VOD/SOS (14% vs 26%)

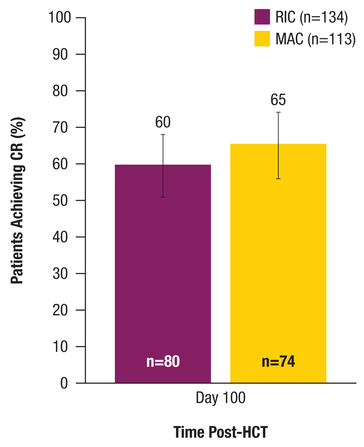
Figure 2. KM-Estimated Day 100 and 1 Year Post-HCT Survival of Patients Receiving RIC or MAC



Whiskers are 95% CI.
CI, confidence interval; HCT, hematopoietic cell transplantation; KM, Kaplan-Meier; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

- KM-estimated day 100 post-HCT survival was 49% (95% confidence interval [CI]: 40%, 57%) in patients receiving RIC and 68% (95% CI: 59%, 76%) in patients receiving MAC
- KM-estimated 1-year post-HCT survival was 34% (95% CI: 26%, 42%) in patients receiving RIC and 48% (95% CI: 38%, 57%) in patients receiving MAC

Figure 3. Day 100 Post-HCT CR of Patients Receiving RIC or MAC



Whiskers are 95% CI.
CI, confidence interval; CR, complete response; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

Table 2. Serious TEAEs of Special Interest

Variable	Patients Receiving RIC (n=134)	Patients Receiving MAC (n=113)
Any Serious TEAEs of Special Interest, n (%)	45 (34)	38 (34)
Infections	29 (22)	14 (12)
Hemorrhages	23 (17)	25 (22)
Coagulopathies	2 (1)	3 (3)
Thromboembolic events	0	2 (2)

MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TEAE, treatment-emergent adverse event.

- Serious treatment-emergent adverse events of special interest were reported in 34% of patients in each subgroup
- Overall, transplant-related mortality by 1 year was 55% in patients treated with RIC (n=74) and 41% in patients treated with MAC (n=46)
- Of all patient deaths, the majority were related to HCT, both for patients treated with RIC (n=74/88, 84%) and MAC (n=46/59, 78%). These included infection (RIC: n=39, 44%; MAC: n=17, 29%) and VOD/SOS (RIC: n=20, 23%; MAC: n=17, 29%)

Conclusions

- Adult patients who receive RIC regimens are still at risk of VOD/SOS, which may be related to characteristics such as older age and previous HCT[4]
  - 45% of patients who received RIC in this analysis had very severe VOD/SOS
- A substantial proportion of patients receiving defibrotide achieved complete resolution of VOD/SOS symptoms in both RIC- and MAC-conditioned groups
- Differences in patient characteristics between those treated with RIC vs MAC, including age, primary disease diagnosis, and donor type, may contribute to differences in VOD/SOS severity and survival
- These results highlight the need to maintain vigilance for VOD/SOS signs and symptoms following RIC, as prompt diagnosis of VOD/SOS may improve outcomes

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