ALL-471

Veno-Occlusive Disease Risk and Other Outcomes in Patients With B-Cell Precursor Acute Lymphoblastic Leukemia Receiving Inotuzumab Ozogamicin and Proceeding to Hematopoietic Stem Cell Transplantation

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Objective

- To evaluate post-HSCT outcomes in adult patients with ALL, and the subset of patients with R/R ALL, who received InO prior to HSCT

Conclusions

- In this real-world population of patients with ALL who received InO prior to HSCT, including heavily pretreated patients, 18-mo OS and NRM were 54% and 22%, respectively
- Common AEs post-HSCT were bacterial infection, viral infection, and acute GVHD
- VOD incidence was consistent with previous reports and dual alkylators should be avoided in patients who receive InO prior to HSCT
- Patients receiving dual alkylators should be considered for clinical trials testing novel prophylactic treatment for post-HSCT endothelial dysfunction syndromes, such as VOD

Electronic Poster and Supplementary Material

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Background

- Inotuzumab ozogamicin (InO) is a CD22-directed antibody–drug conjugate indicated for adults with relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL)[1-3]
- InO was approved based on findings from the phase 3 INO-VATE ALL trial, which demonstrated higher rates of complete remission (CR) or CR with incomplete hematologic recovery (CRi) in InO-treated patients compared with standard of care therapy[4]
- InO has been associated with hepatotoxicity and hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), particularly following hematopoietic stem cell transplantation (HSCT)[3]
- A post-marketing requirement was agreed with the US Food & Drug Administration (FDA) to characterize 180-d HSCT toxicity in patients receiving InO over at least a 5-y period

Methods

STUDY DESIGN AND PATIENTS

- This observational, post-authorization safety study included US patients aged ≥18 y with B-cell precursor ALL treated with InO who received subsequent HSCT at a participating center with data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR)
- We report outcomes in all adults with ALL who received InO, with a particular focus on the subset of adults with R/R ALL who proceeded to first allogeneic HSCT
  - The subset included all patients ≥18 y who had R/R B-cell ALL and received InO prior to HSCT
- The current analysis is based on 5-y data accrued from August 18, 2017 to the data lock date of August 17, 2022

ANALYSES

- Post-HSCT outcomes included overall survival (OS), non-relapse mortality (NRM), relapse, and adverse events (AEs)
- Multivariate analyses analyzed prognostic factors for NRM and VOD/SOS

Results

PATIENTS

- 261 adult patients with ALL (median age 39 y, 58% were male) received InO and proceeded to first allogeneic HSCT (**Table 1** and **Supplementary Table S1**)
- **Additional details are in the Supplementary Material, downloaded using the QR code**
- Prior to HSCT:
  - 36% were in first complete remission (CR1), 46% in CR2, 11% in CR≥3
  - 4% were in first relapse, 1% in ≥3rd relapse, and 2% with primary induction failure
  - 32%, 47%, 14%, 5%, and <1% received 1, 2, 3, 4, and 5 InO cycles, respectively
  - 120 and 112 patients received InO as monotherapy or in combination with other agents, respectively (data unavailable in 29 patients)
- CR/CRi and MRD negativity (as a percentage of patients with CR/CRi) was achieved in 80% and 80% of patients, respectively, after InO treatment
- Median (range) time from last InO dose to HSCT was 2.4 (0.6–26.2) mo

Table 1: Demographics and baseline characteristics

	Patients with ALL (N=261[a])	Patients with R/R ALL (N=166)
Disease status prior to HSCT, n (%)		
CR1	94 (36)	0 (0)
CR2	121 (46)	121 (73)
CR ≥3	28 (11)	28 (17)
1st relapse	10 (4)	10 (6)
≥3rd relapse	3 (1)	3 (2)
Primary induction failure	4 (2)	4 (2)
Not reported	1 (<1)	0 (0)
Lines of therapy prior to HSCT, n (%)		
First line	8 (3)	0 (0)
Salvage 1	57 (22)	19 (11)
Salvage 2	59 (23)	39 (23)
Salvage >2	114 (44)	89 (54)
Not reported	23 (10)	19 (11)
Median (range)	3 (1–10)	4 (2–10)
Lines of therapy prior to InO, n (%)		
No treatment given	28 (11)	6 (4)
First line	71 (27)	26 (16)
Salvage 1	47 (18)	39 (23)
Salvage 2	44 (17)	39 (23)
Salvage >2	42 (16)	33 (20)
Not reported	29 (11)	23 (14)
Median (range)	2 (0–8)	3 (0–8)
Cycles of InO, n (%)		
1	83 (32)	54 (32)
2	122 (47)	77 (46)
3	37 (14)	24 (15)
4	13 (5)	7 (4)
5	1 (<1)	1 (1)
Not reported	5 (2)	3 (2)
InO administration, n (%)		
Single agent	120 (46)	81 (49)
Combined with other chemotherapy/systemic therapy	112 (43)	62 (37)
Not reported	29 (11)	23 (14)
Time from last InO dose to HSCT, median (range), mo	2.4 (0.6–26.2)	2.3 (0.6–26.2)
Conditioning regimen intensity, n (%)		
Myeloablative	135 (52)	88 (53)
Reduced intensity/non-myeloablative	113 (43)	70 (42)
Unknown	5 (2)	3 (2)
Not reported	8 (3)	5 (3)

[a] Data available for disease status, n=260; lines of therapy prior to HSCT, n=241; lines of therapy prior to InO, n=232; cycle of InO, n=256; regimen containing InO, n= 232; response to InO, n=256; and conditioning regimen intensity, n=248.
ALL=acute lymphoblastic leukemia; ANC=absolute neutrophil count; BMI=body mass index; CR=complete remission; CR1/CR2/CR3=first/second/third complete remission; HSCT=hematopoietic stem cell transplantation; InO=inotuzumab ozogamicin; R/R=relapsed/refractory

CLINICAL OUTCOMES

- Post-HSCT outcomes are shown in 244 patients with ALL, including 156 patients with R/R ALL (**Table 2**)
- Median (range) of follow-up was 10.6 (0.4–54.1) and 8.8 (0.4–50.8) mo in adults with ALL and R/R ALL, respectively
- Post-HSCT OS at 18 mo was 54% in patients with ALL and 50% in patients with R/R ALL (**Supplementary Figure S1**)
- NRM at 18 mo was 22% in patients with ALL and 25% in patients with R/R ALL (**Figure 1**)
  - The most common causes (≥10%) in 244 patients with ALL were VOD/SOS (26%; n=13), graft-versus-host disease (GVHD; 22%; n=11), organ failure (20%; n=10), and infection (10%; n=5)
  - The most common causes (≥10%) in 156 patients with R/R ALL were VOD/SOS (24%; n=9), GVHD (19%; n=7), organ failure (19%; n=7), and interstitial pneumonitis (11%; n=4)

ADVERSE EVENTS

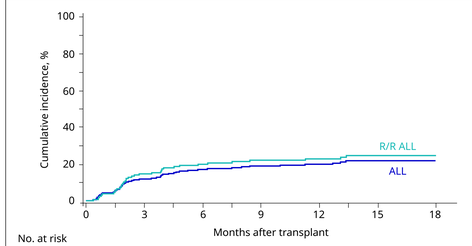
- AEs occurring in ≥30% of patients with ALL within 100 d post-HSCT were bacterial infection (51%), viral infection (44%), and acute GVHD (grades II–IV; 43%)
  - Corresponding rates in patients with R/R ALL were 56%, 44%, and 41%
- Within 100 d post-HSCT, 14% of patients with ALL and 17% of patients with R/R ALL had VOD/SOS (**Figure 2**)
  - Corresponding mortality rates were 36% and 40% among those who developed VOD/SOS, and 9% and 10% as a percentage of all patients (**Table 2**)

Table 2: Post-HSCT outcomes

Outcome	Patients with ALL (N=244)	Patients with R/R ALL (N=156)
Follow up, median (range), mo	10.6 (0.4–54.1)	8.8 (0.4–50.8)
12-mo overall survival, % (95% CI)	61 (54–67)	56 (47–64)
18-mo overall survival, % (95% CI)	54 (47–61)	50 (41–58)
12-mo NRM, % (95% CI)	20 (15–25)	23 (17–30)
18-mo NRM, % (95% CI)	22 (17–27)	25 (18–32)
12-mo non-transplant-related mortality, % (95% CI)	19 (14–25)	21 (15–28)
18-mo non-transplant-related mortality, % (95% CI)	24 (19–31)	25 (18–33)
12-mo relapse, % (95% CI)	33 (27–39)	34 (26–42)
18-mo relapse, % (95% CI)	40 (33–47)	40 (32–48)
Continued CR[a], n (%)	226 (93)	138 (88)
VOD/SOS incidence within 100 d, % (95% CI)	14 (10–19)	18 (12–24)
Median (range) time from HSCT to VOD/SOS, mo	0.5 (0.2–3.0)	0.4 (0.2–2.6)
VOD/SOS mortality among pts who developed VOD/SOS, % (% of all pts)	36 (9)	40 (10)

[a] Continued CR defined as a patient who received HSCT during CR, and CR is sustained post HSCT.
ALL=acute lymphoblastic leukemia; CR=complete remission; HSCT=hematopoietic stem cell transplant; NRM=non-relapse mortality; OS=overall survival; R/R=relapsed/refractory; VOD/SOS=veno-occlusive disease/sinusoidal obstruction syndrome

Figure 1: NRM within 18 mo post HSCT



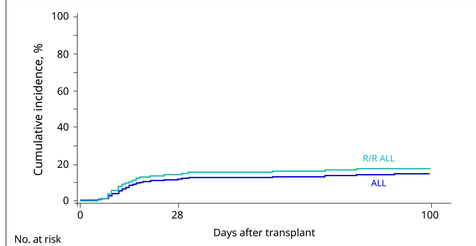
ALL=acute lymphoblastic leukemia; HSCT=hematopoietic stem cell transplant; NRM=non-relapse mortality; R/R=relapsed/refractory

- Of 35 adults with ALL who developed VOD/SOS, 15 cases were mild, 20 were severe, and 22 died within 18 mo post-HSCT
- Of 35 adults with ALL who developed VOD/SOS, 8 patients received prophylactic defibrotide (of all 244 patients, 22 received defibrotide)
- VOS/SOS incidence within 100 d post-HSCT was 20%, 17%, 10%, and 16% in patients with cumulative InO doses of <1.8, 1.8–2.7, 2.8–3.2, and ≥3.3 mg/m^2, respectively
- VOS/SOS incidence within 100 d post-HSCT was not estimable (NE), 22%, NE, and 16% in patients who received InO as a single agent with cumulative doses of <1.8, 1.8–2.7, 2.8–3.2, and ≥3.3 mg/m^2, respectively
- VOS/SOS incidence within 100 d post-HSCT was 18%, 9%, NE, and NE in patients who received InO with other agents with cumulative InO doses of <1.8, 1.8–2.7, 2.8–3.2, and ≥3.3 mg/m^2, respectively
- VOS/SOS incidence within 100 d post HSCT was 15%, 25%, 17%, and 14% in patients with time from last InO dose to HSCT of <1, 1.1–1.6, 1.7–3, and ≥3 mo, respectively

MULTIVARIATE ANALYSES

- Overall, 204 patients with ALL (adult patients with at least 12 mo of follow-up) were included in the multivariate analyses (**Supplementary Table S2**)
- Karnofsky score <90 or unknown and dual alkylators were negative prognostic factors for NRM at 18 mo
- Dual alkylators were the only negative prognostic factor for VOD/SOS at 100 d (P=0.0131)
- Notably, there was no difference for VOD risk for reduced-intensity conditioning vs myeloablative conditioning, if dual alkylators were excluded

Figure 2: Cumulative incidence of VOD/SOS within 100 d post HSCT



ALL=acute lymphoblastic leukemia; HSCT=hematopoietic stem cell transplant; R/R=relapsed/refractory; VOD/SOS=veno-occlusive disease/sinusoidal obstruction syndrome