

Impact of inotuzumab ozogamicin on outcome in relapsed or refractory acute B-cell lymphoblastic leukemia patients prior to allogeneic hematopoietic stem cell transplantation and risk of sinusoidal obstruction syndrome/venous occlusive disease

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Abstract

We evaluated 58 patients with relapsed or refractory (r/r) acute B-lymphoblastic leukemia (B-ALL; median age 42.5 years; range, 16-69 years), treated with inotuzumab ozogamicin (INO) between 2016-2022 and who received an allogeneic hematopoietic stem cell transplantation (allo-HCT) consecutively. Forty-seven (81%) of the 58 patients were heavily pretreated receiving intensive chemotherapy +/- tyrosine kinase inhibitor, blinatumomab in 24 (41%) and allo-HCT at first-line in 11 (19%) patients. Complete remission rate prior to allo-HCT was 84%. Median follow-up was 30.5 months and median overall survival (OS) measured from start of INO was 11.2 months. One- and 2-year OS rates were 50% (95% confidence interval [CI]: 38.4-56.1) and 36.7% (95% CI: 25.5-52.9), respectively. Sinusoidal obstruction syndrome/venous occlusive disease (SOS/VOD) after allo-HCT occurred in 17 (29%) patients. Of those, nine (53%) patients died due to SOS/VOD and multi-organ failure. Two had received >2 INO cycles (3 cycles, 5 cycles, N=1, each), all others ≤2 INO cycles prior to allo-HCT. Logistic regression analysis revealed conditioning with double alkylators ($P=0.038$) and allo-HCT during first-line therapy ($P=0.050$)

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as significant risk factors for SOS/VOD and in trend allo-HCT ≤ 60 days from last INO application ($P=0.07$), whereas number of INO cycles before allo-HCT and time between last INO application and allo-HCT were not significant. Relapse/progressive disease occurred in 20 (34%) patients. Of those, five (25%) patients are still alive, whereas 15 succumbed of their disease. Treatment with INO seems to be an effective approach with successful bridge-to-transplant. However, risk of SOS/VOD is high, necessitating continuous monitoring and recognition of SOS/VOD risk factors.

Introduction

Refractory/relapsed (r/r) B-cell acute lymphoblastic leukemia (B-ALL) in adults has a dismal prognosis, with less than 10% of patients being long-term survivors.¹ At present, allogeneic hematopoietic stem cell transplantation (allo-HCT) is considered the only curative option for patients with r/r B-ALL with best outcomes achieved after effective salvage re-induction therapy and transplantation in complete remission (CR) without measurable residual disease (MRD).^{2,3} The role of novel immune-based chimeric antigen receptor (CAR) T-cell infusions in this setting has remained undefined.⁴⁻⁶ Although conventional salvage chemotherapy is capable of inducing CR rates of 18% to 44% in patients with r/r B-ALL,⁷⁻¹³ antibody-based strategies using inotuzumab ozogamicin (INO) or blinatumomab have been proved to be more effective.^{14,15} INO is a humanized anti-CD22 monoclonal antibody conjugated to the potent cytotoxic agent calicheamicin, which was developed as a targeted therapy for B-cell malignancies.^{16,17} Upon binding to CD22 and internalization, calicheamicin is off-set and binds to the DNA, thereby leading to double-strand breaks and apoptosis.^{16,17}

The phase III INO-VATE trial demonstrated superior efficacy of INO as compared to standard of care (SoC) treatment for r/r B-ALL, inducing CR or CR with incomplete hematological recovery (CRi) in 80.7% versus 29.4% of the patients ($P<0.001$), respectively.¹⁵ Additionally, the rate of MRD negativity (0.01% marrow blasts assessed at a central laboratory with the use of multicolor, multiparameter flow cytometry) in patients with CR/CRi was significantly higher after treatment with INO as compared to SoC (78.4% vs. 28.1%; $P<0.001$). After INO treatment, 41% of patients proceeded directly to allo-HCT as compared to 11% after SoC ($P<0.001$). Median progression-free survival was significantly longer after INO as compared to SoC (5.0 months vs. 1.8 months; $P<0.001$). Median overall survival (OS) was 7.7 months after INO as compared to 6.2 months after SoC, and the 2-year OS rates were 23% versus 10%, respectively.¹⁵ Taken together, deep remissions with MRD-negative status can be achieved with INO treatment in patients with r/r B-ALL. Nevertheless, remissions are not durable, necessitating further consolidation approaches, such as allo-HCT.

Sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease (VOD), is a potentially life-threatening complication of allo-HCT.¹⁸ Rates of SOS/VOD may be further increased after pretreatment with INO.¹⁹ Within

the INO-VATE trial, the most frequent grade 3 or higher non-hematologic adverse events after INO were liver-related.¹⁵ Of the 77 patients who received INO and proceeded to allo-HCT, 17 (22%) had SOS/VOD; of those, five events were fatal. Of 32 patients who received SoC and proceeded to HSCT, one (3%) experienced SOS/VOD that was ongoing at the time of death due to septic shock.²⁰

The objectives of our study were to characterize a series of adult r/r B-ALL patients and evaluate outcome after treatment with INO with a particular focus on risk of SOS/VOD.

Methods

Information on 58 patients (adolescent N=1; adult N=57) (median age, 42.5 years; range, 16-69 years) with histologically confirmed r/r B-ALL, who were treated with INO between 2016 and 2022 within a compassionate use program (N=7) or in-label after approval by the Food and Drug Administration (FDA) or the European Medical Agency (EMA) (N=51) was collected from eleven institutions in the US and Europe. All 58 patients were CD22-positive at relapse/progressive disease.

Participating centers were chosen upon network relationships of the first and last author. Detailed case report forms (including information on baseline characteristics, chemotherapy, allo-HCT, response, and survival) were collected from all participating centers. Inclusion criteria were adult r/r B-ALL patients and treatment with INO prior to allo-HCT. All patients who fulfilled these criteria were included by the participating institutions. Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.²¹ Flow cytometry and quantitative polymerase chain reaction (qPCR) of leukemia-specific rearrangements of *BCR::ABL1* transcript levels were used to monitor MRD. Data collection and analyses were approved by the Institutional Review Boards of the participating centers.

Statistical analyses

Comparisons of patient characteristics were performed with the Kruskal-Wallis rank sum test for continuous variables and Fisher's exact test for categorical variables. In order to identify prognostic variables with respect to occurrence of SOS/VOD after allo-HCT logistic regression models were used. The median follow-up time was computed using

the reverse Kaplan-Meier estimate.²² The Kaplan-Meier method was used to estimate the distribution of OS.²³ OS was calculated from start of INO treatment until last follow-up or death. Confidence interval (CI) estimation for survival curves was based on the cumulative hazard function using Greenwood's formula for variance estimation. Log-rank tests were employed to compare survival curves between groups. Cumulative incidences of relapse (CIR) and death (CID) and their standard errors were computed according to the method described by Gray²⁴ and included only patients attaining complete remission. CIR and CID were calculated from achievement of CR after start of INO treatment until relapse or death. In patients proceeding to allo-HCT without achieving a CR or CRi (N=10), the date of transplant was set per definition as start date to calculate CIR and CID. In addition to the univariable tests, an exploratory Cox regression analysis was performed to evaluate prognostic variables on OS measured from the date of allo-HCT including the following covariates: age, sex, allo-HCT during first-line therapy, prior treatment with blinatumomab, time from treatment with INO to allo-HCT (dichotomized ≤ 50 days vs. > 50 days), number of INO cycles before allo-HCT (dichotomized ≤ 2 cycles vs. > 2 cycles), remission status at allo-HCT (dichotomized CR/CRi vs. no-CR), conditioning regimen (myeloablative vs. RIC), donor type (matched unrelated donor/matched related donor vs. other including haplo-identical and cord blood). Backward selection applying a stopping rule based on *P* values was used in the multivariable Cox regression model to exclude redundant or unnecessary variables.²⁵ All statistical analyses were performed with the statistical software environment R, version 3.3.1, using the R packages rms including hmisc, lattice, ggplot2 and Formula and survival.²⁶

Results

Patient characteristics

At the time of r/r B-ALL, median white blood cell and platelet counts were $5.9 \times 10^9/L$ (range, $0.2-127 \times 10^9/L$) and $104.5 \times 10^9/L$ (range, $6-400 \times 10^9/L$), respectively. Median blast cell count in bone marrow was 30% (range, 0-98%). Twenty (34%) patients were female; ECOG was 0 in 32 (55%), 1 in 16 (28%), 2 in two (3%) patients and missing in eight (14%) patients (Table 1). Twelve (23%) of 52 patients had extramedullary disease (missing data, N=6).

Genetics

Cytogenetic analysis at the time of diagnosis of ALL was available in 48 (83%) patients. Of those, 16 patients displayed a t(9;22)(q34;q11), 13 patients had a normal karyotype, 13 were complex (≥ 3 abnormalities),²⁷ and six had other abnormalities.

At relapse, cytogenetic analysis was available in 23 patients (40%). Seven patients displayed a t(9;22), eight had

Table 1. Patient characteristics at the time point of relapsed/refractory acute lymphoblastic leukemia.

Total patients N=58		
Characteristic	Value	% or range
Sex: Female, N	20	34
Median age in years	42.5	16-69
Median WBC $\times 10^9/L$ missing, N	5.9 10	0.2-127 -
Median platelets $\times 10^9/L$ missing, N	104.5 10	6-400 -
Median hemoglobin, g/dL missing, N	11.8 10	6.6-15.6 -
Median LDH, U/L missing, N	327 12	119-3,665 -
Median BM blasts, % missing, N	30 7	0-98 -
ECOG PS, N		
0	34	59
≤ 2	18	31
missing	6	10
Cytogenetics, N		
normal	13	21
t(9;22)	17	28
complex	14	23
other	6	10
missing	11	18

LDH: lactate dehydrogenase; BM: bone marrow; ECOG PS: Eastern Cooperative Oncology Group performance status; WBC: white blood cell count.

a normal karyotype, three were complex and five had other abnormalities. One patient with a normal karyotype at diagnosis showed a clonal evolution to a complex karyotype (trisomy 14, trisomy 21 and an additional X-chromosome). Two patients with prior t(9;22) displayed a normal karyotype at relapse. In those patients with t(9;22) at diagnosis but without cytogenetic analysis at relapse (N=8), *BCR::ABL* was confirmed by PCR. Of the 13 patients with a complex karyotype at diagnosis, two were still complex, three had a normal karyotype, two displayed other, new abnormalities (trisomy 5; *KMT2* rearrangement, N=1, each) and six were not analyzed.

Prior treatment

One (2%) of the 58 patients was previously treated with tyrosine kinase inhibitor (TKI) for chronic myeloid leukemia and progressed to *BCR::ABL* positive blast cell crisis of B-lymphoid lineage. Forty-seven (81%) of the 58 patients were heavily pretreated receiving intensive chemotherapy +/- TKI, whereas 11 (19%) received TKI +/- glucocorticoids. Overall, blinatumomab was administered in 24 (41%) patients. Of those, two patients received blinatumomab at first line and achieved CR (blinatumomab + dasatinib for

BCR::ABL positive ALL, N=1; sequential chemotherapy and blinatumomab, LAL2317 trial; *clinicaltrials.gov*. Identifier: NCT03367299; N=1). Three patients were primary refractory after first-line chemotherapy. Of those, two achieved CR after blinatumomab, whereas one patient was refractory after salvage with blinatumomab. Finally, in five patients blinatumomab was given to achieve MRD negativity after first-line chemotherapy. In 14 patients blinatumomab was given at relapse prior to INO. Of those, 11 were refractory and three achieved CR.

Treatment with inotuzumab ozogamicin

INO was dosed at 0.8 mg/m² body surface area (BSA) and applied as an intravenous infusion over 1 hour on day 1 and at 0.5 mg/m² of BSA on days 8 and 15. Once the patients had achieved CR, the dose on day 1 of each consecutive cycle was reduced to 0.5 mg/m² BSA. Up to six INO cycles (≤ 2 cycles, N=52; 3-4 cycles, N=4; 5-6 cycles, N=2) were administered according to the previously approved regimen. The patient with *BCR::ABL* positive blast cell crisis of B-lymphoid lineage received TKI in addition to INO. Extramedullary disease response assessment was performed by computed tomography (CT) or positron emission tomography-computed tomography (PET-CT). SOS/VOD was assessed according to previously defined clinical criteria and diagnosed by the treating investigator.¹⁵

Response

Response assessment was performed in 53 (91%) patients after the first INO cycle. Of those, 39 (74%) patients achieved CR, five (9%) a partial remission (PR), whereas nine (17%) were refractory (RD). Prior to allo-HCT, 49 (84%) achieved CR, four (7%) PR and four (7%) had RD. Two patients not achieving a response to INO achieved CR at the date of allo-HCT, one after 1.5 cycles binatumumab and one after two cycles HyperCVAD. One (2%) patient relapsed prior to allo-HCT. This patient received high-dose Ara-C and mitoxantrone as well as two cycles blinatumomab and achieved CR again. Thus, at time of allo-HCT 49 patients were in CR. Four patients received blinatumomab (1 cycle, N=3, 2 cycles, N=1) as treatment of MRD prior to allo-HCT. Of those, one was MRD-negative prior to allo-HCT. One patient received maintenance in CR with vincristine, methotrexate (MTX) and 6-mercaptopurine prior to allo-HCT.

Measurable residual disease response

MRD data after INO prior to allo-HCT were available in 44 (90%) of 49 responding patients. Of those, 26 (59%) were MRD-negative, 16 (36%) were MRD-positive and two (5%) had non-quantifiable but detectable MRD below 0.01%.

Allogeneic hematopoietic stem cell transplantation and maintenance after allogeneic hematopoietic stem cell transplantation

Twenty-five (43%) patients received myeloablative and

33 (57%) reduced-intensity conditioning. Furthermore, conditioning regimen consisted of double alkylators in 17 patients (29%). Type of donor were matched-related siblings in 11 (19%), matched-unrelated in 22 (38%), and haplo-identical/cord blood in 25 (43%) patients, respectively. Time between INO and allo-HCT was in median 50 days (range, 25-374 days).

Overall, maintenance after allo-HCT was performed in seven patients. Of those, three patients were *BCR::ABL* MRD-positive and were treated with either ponatinib (N=2) or dasatinib (N=1). Additionally one patient with MRD-positive disease prior to allo-HCT received three cycles blinatumomab and three DLI infusions due to progression of MRD after allo-HCT. One patient who was *BCR::ABL* MRD-negative prior to allo-HCT received maintenance with ponatinib as relapse prevention. Two patients received one cycle blinatumomab as maintenance therapy after allo-HCT. Both were MRD-negative pretransplant and at the time of blinatumomab maintenance.

Survival

Median follow-up was 30.5 months (95% CI: 25.7-42.5) and median OS measured from start of INO was 11.2 months (95% CI: 7.59-37.1; Figure 1). One-year and 2-years OS rates were 50% (95% CI: 38.4-56.1) and 36.7% (95% CI: 25.5-52.9), respectively. In univariable Cox regression analysis age as a continuous variable had no impact on OS ($P=0.98$). This was also true when using 60 years as cutoff ($P=0.81$). Prior to allo-HCT, 52 patients received ≤ 2 , four patients 3-4 INO cycles and two patients 5-6 INO cycles.

Relapse/progressive disease occurred in 20 (34%) patients. Of those, five (25%) patients are still alive, whereas 15 succumbed of their disease.

Twenty-one patients died in remission (cause of death: SARS-CoV2 infection, N=2; graft-versus-host disease, N=2; multi-organ failure, N=4; septic infection, N=4; SOS/VOD, N=9) and 17 are in ongoing CR leading to a CIR of 35.0% (95% CI: 21.9-48.1) and CID of 37.6% (95% CI: 24.6-50.1; Figure 2) after 2 years.

Our cohort included also six patients with central nervous system (CNS) involvement at diagnosis, all of whom received CNS treatment with MTX, cytarabine and dexamethasone until CR. Of those, only one had CNS involvement at relapse. This patient received CNS radiation. Additionally, seven patients had a CNS involvement at relapse, which was treated with high-dose MTX and high-dose Ara-C (N=1), intrathecal MTX, cytarabine and dexamethasone and/or radiation (N=6).

A multivariable model evaluating OS after allo-HCT revealed number of INO cycles > 2 (hazard ratio [HR]=0.220; 95% CI: 0.047-1.039; $P=0.056$), remission at date of allo-HCT (HR=0.544; 95% CI: 0.249-1.190; $P=0.128$), allo-HCT during first line therapy (HR=2.351; 95% CI: 0.962-5.744; $P=0.061$) and pretreatment with blinatumomab (HR=2.190; 95% CI: 1.078-4.449; $P=0.030$) in the final model after limited

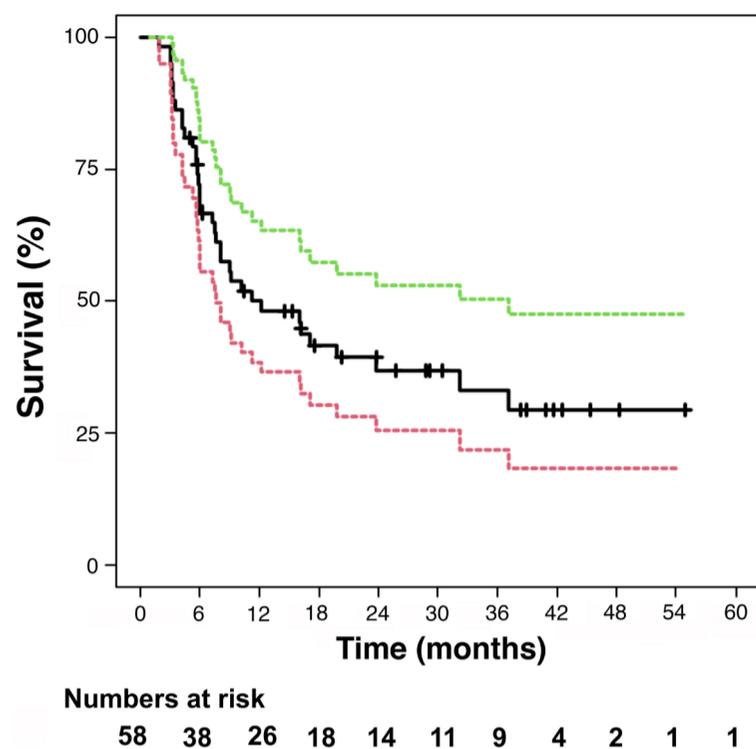


Figure 1. Overall survival of relapsed/refractory patients with B-acute lymphoblastic leukemia after treatment with inotuzumab ozogamicin. Green and red dotted lines indicate upper and lower 95% confidence interval.

backward selection, whereas time interval between start INO and allo-HCT, sex, type of conditioning regimen, donor type and age were excluded.

Sinusoidal obstruction syndrome/venous occlusive disease

SOS/VOD after allo-HCT occurred in 17 (29%) patients. Of those, nine (53%) patients died due to VOD with multi-organ failure. One had received five INO cycles and another one three INO cycles, all other received ≤ 2 INO cycles prior to allo-HCT. Seven (28%) of the 25 patients with myeloablative conditioning experienced SOS/VOD which was fatal in two patients. In comparison, SOS/VOD occurred in ten (30%) of 33 patients after reduced-intensity conditioning and was fatal in seven patients. Regarding conditioning regimen consisting of double alkylators, SOS/VOD occurred in eight (50%) of 16 patients, which was fatal in five patients. In contrast, SOS/VOD occurred in nine (21%) of 42 patients not treated with double alkylators as conditioning regimen, which was fatal in four patients.

SOS/VOD occurred in median after 61 days (range, 25-126 days) after last INO application and after 13 days (range, 5-42 days) after allo-HCT (Table 2).

In univariable logistic regression analysis risk factors for SOS/VOD were conditioning with double alkylators (OR, 3.67; 95% CI: 1.08-12.50; $P=0.038$), allo-HCT during first-line therapy (OR, 3.97; 95% CI: 1.00-15.39; $P=0.050$) and in trend allo-HCT ≤ 60 days from last INO application (OR, 4.74, 95% CI: 0.91-24.65, $P=0.07$), whereas more than two INO cycles before allo-HCT ($P=0.82$) was not significant. Further variables, such as age, sex, donor, dose intensity of conditioning or remission status before allo-HCT had

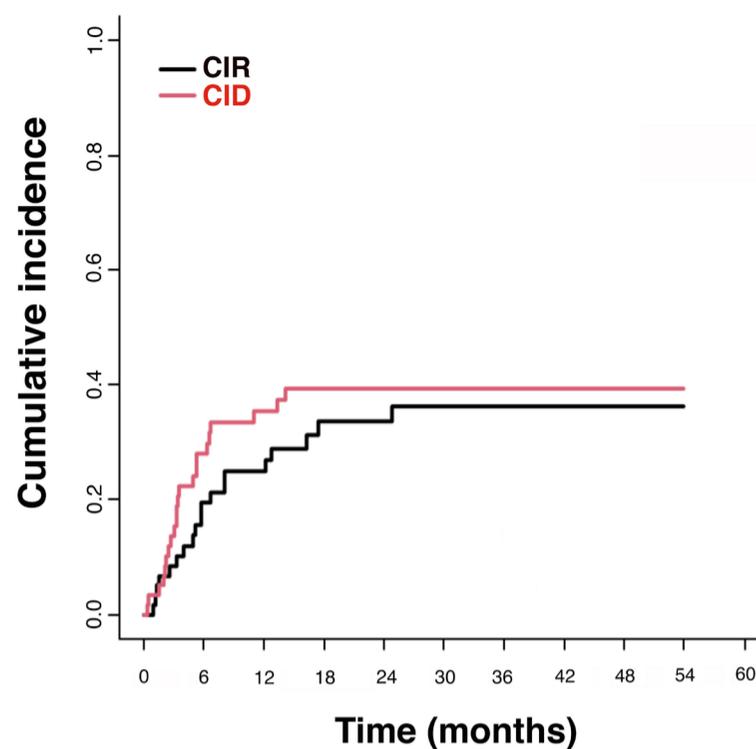


Figure 2. Cumulative incidence of relapse and cumulative incidence of death. Cumulative incidence of relapse (CIR) and cumulative incidence of death (CID) included only patients achieving complete remission.

no impact in univariable assessment.

Discussion

The occurrence of SOS/VOD is a potentially life-threatening complication of allo-HCT²⁸ with a mortality rate of up to 84.3%.²⁹ Moreover, the risk of SOS/VOD following allo-HCT is even increased after INO exposure leading to the recommendation that patients being bridged to allo-HCT be treated with two or fewer cycles of INO (3 cycles if necessary to achieve an MRD-negative CR/CRi).^{19,20,30} In our cohort, SOS/VOD occurred in 17 (29%) patients and was fatal in nine (53%), which is higher than that reported from the INO-VATE trial, particularly the rate of fatal outcome.¹⁵ Such a higher occurrence might be explained, at least in part, by the real-life setting of this study, where INO was administered in a time window in which guidelines on SOS/VOD prevention and management in patients treated with this antibody were not yet available¹⁹ and involved physicians were still on a learning curve.

A large number of our patients (81%) were heavily pretreated including allo-HCT at first-line therapy in 19% of the patients. Our real-life data confirm the detrimental effect of double alkylator conditioning for patients undergoing allo-HCT previously treated with INO, a feature that we now recognize as one of the most important risk factors for the development of SOS/VOD in this treatment setting.^{20,31} In addition, we also identified allo-HCT during first-line therapy and in trend allo-HCT ≤ 60 days after INO as risk factors for SOS/VOD. In contrast to previous data more than two INO cycles before allo-HCT was not significant.¹⁵

Table 2. Clinical characteristics of the patients with occurrence of sinusoidal obstruction syndrome/venous occlusive disease after allogeneic hematopoietic stem cell transplantation.

Patient N	Age in years	Sex	ECOG PS	Grade of SOS/ VOD	Allo-HCT at first line	N of INO cycles	Days of SOS/VOD occurrence after last INO application	Myeloablative conditioning	Dual alkylators for conditioning	Days of SOS/ VOD occurrence after allo-HCT
1	56	F	1	1	No	2	71	Yes	Yes	25
2	46	M	0	1	No	2	126	Yes	No	42
3	46	F	0	2	Yes	3	76	No	No	27
4	28	M	1	4	No	2	45	Yes	No	17
5	30	M	1	3	No	1	58	Yes	No	10
6	43	M	1	4	Yes	2	61	No	Yes	5
7	36	F	1	4	No	1	40	Yes	Yes	9
8	58	M	0	5	Yes	2	59	Yes	Yes	11
9	28	F	0	5	Yes	1.67	25	No	Yes	10
10	54	M	1	5	No	5	44	No	No	18
11	28	M	1	5	No	2	104	No	No	14
12	40	M	1	5	Yes	2	118	No	No	34
13	49	F	1	5	No	1	73	Yes	No	11
14	31	M	0	5	No	2	35	No	Yes	8
15	36	F	0	5	Yes	2	70	No	Yes	9
16	56	M	0	5	No	2	35	No	Yes	13
17	23	M	0	3	No	1	61	No	No	13

Allo-HCT: allogeneic hematopoietic stem cell transplantation; INO: inotuzumab ozogamicin; SOS/VOD: sinusoidal obstruction syndrome/venous occlusive disease, M: male; F: female; ECOG PS: Eastern Cooperative Oncology Group performance status.

However, one limitation of this study is the fact that in our cohort only a small fraction of the patients had received ≥ 3 INO cycles prior to allo-HCT.

While the rate of SOS/VOD after myeloablative and reduced intensity conditioning was comparable in our cohort, the rate of fatal SOS/VOD outcome was higher in patients after reduced intensity conditioning, which contrasts previous data.¹⁸ If prophylactic treatment with defibrotide, as recommended in the pediatric setting,³² might have reduced the rate of VOD, remains elusive.^{31,33}

The CR/CRi rate in our cohort was higher than that reported from the INO-VATE trial (84% as compared to 73.8%)³⁴ and other real-world data.³⁵ However, in our cohort, the MRD-negative rate was lower as compared to that of the INO-VATE trial. This might be related to the fact that in our study, MRD was evaluated either by flow cytometry or PCR for *BCR::ABL* with a threshold of 0.01% to 0.0001% as compared to that of the INO-VATE trial, where MRD was measured by flow cytometry with a threshold of 0.01% bone marrow blasts.¹⁵

In contrast to recently published data,³⁶ we observed a negative effect of previous blinatumomab exposure, which might be related to an exhaustion of CD3 lymphocyte effector T cells.

Although our study included only patients who went on to allo-HCT after INO, the higher CR/CRi rate did not translate to a longer median OS as compared to that from the INO-

VATE trial (11.2 months vs. 12.6 months),³⁴ mainly caused by a high rate of CIR and CID. Despite an MRD positivity rate of 36% (N=16), maintenance after allo-HCT was performed in our study in only seven patients, mainly due to acute graft-versus-host disease or relapse. If maintenance therapy after allo-HSCT, e.g., with blinatumomab, might be beneficial, as shown after treatment with blinatumomab in MRD-positive patients prior to allo-HSCT,³⁷ remains elusive and needs to be evaluated in a larger cohort, ideally in a prospective trial.

Treatment with INO seems to be an effective approach with successful bridge-to-transplant, but further consolidation approaches, such as chimeric antigen receptor T cells or advanced bi-specific antibodies are warranted to prolong OS.

Our analysis has several limitations. Since this is a retrospective, non-randomized cohort analysis no direct comparison to outcome of r/r B-ALL after standard of-care chemotherapy treatment was feasible. However, since a large fraction of the patients (81%) were heavily pretreated with intensive chemotherapy \pm TKI including prior allo-HCT in 19% of the patients, standard-of-care chemotherapy would have likely failed to induce a remission. In addition, retrospectively collected data have serious limitations since the factors for allocating patients to allo-HCT, such as co-morbidities, individual assessment of the treating physician, choice of conditioning, and availability of a do-

nor, remain unknown, and this needs to be taken into account when evaluating the value of allo-HCT in our series. Furthermore, data on patients treated with INO without allo-HCT were not part of our analysis.

Conclusions

Treatment with INO seems to be an effective approach with successful bridge-to-transplant. However, further consolidation approaches, such as chimeric antigen receptor T cells or advanced bi-specific antibodies are warranted to prolong OS. In addition, risk of SOS/VOD is not negligible, necessitating continuous monitoring, recognition of SOS/VOD risk factors, such as double alkylating agents as conditioning regimen prior to allo-HCT and guidelines application to mitigate its incidence.³⁸ In particular, the addition of a second alkylating agent into the conditioning regimen must be avoided.

Disclosures

No conflicts of interest to disclose.

Contributions

SK and CP were responsible for the concept of this paper, contributed to the literature search data collection, contributed patients, analyzed and interpreted data, and critically revised the manuscript. RFS was responsible for the concept of this paper, analyzed and interpreted data, and wrote the manuscript. CS, FG, AB, JW, PC, FS, SG, LP, EB, GM, IZ, MC, PS, FR, MA, and MJL contributed patients and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Data-sharing statement

Questions regarding data sharing should be addressed to the corresponding author.

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