Outcome of relapsed or refractory acute B-lymphoblastic leukemia patients and BCR-ABL positive blast cell crisis of B-lymphoid lineage with extramedullary disease receiving inotuzumab ozogamicin

by Sabine Kayser, Chiara Sartor, Marlise R. Luskin, Jonathan Webster, Fabio Giglio, Nydia Panitz, Andrew M. Brunner, Matthias Fante, Christoph Lutz, Daniel Wolff, Anthony D. Ho, Mark J. Levis, Richard F. Schlenk, and Christina Papayannidis

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Outcome of relapsed or refractory acute B-lymphoblastic leukemia patients and $BCR-ABL$ positive blast cell crisis of B-lymphoid lineage with extramedullary disease receiving inotuzumab ozogamicin

Running title: Outcome of r/r B-ALL with extramedullary disease

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ABSTRACT

Acute lymphoblastic leukemia (ALL) can relapse in the extramedullary compartment, with or without medullary involvement. Response to treatment may be unique. We evaluated response to inotuzumab ozogamicin (INO) in 31 relapsed/refractory (r/r) B-ALL patients with extramedullary disease (EMD). Median age was 31 (range, 19-81) years. All patients were heavily pretreated, including allogeneic hematopoietic stem cell transplantation (allo-HCT; n=18). Overall response rate after two INO cycles was 84% (complete remission (CR), 55%; partial remission (PR), 29%; resistant disease (PD), 13%; early death, 3%). Median follow-up was 29 months and median overall survival (OS) 12.8 months. One-year and 2-year OS rates were 53% (95%-CI, 37-76%) and 18% (95%-CI, 8-43%), respectively. Age had no impact on OS when assessed as a continuous variable or dichotomized at 60 years. Twelve patients proceeded to allo-HCT (CR, n=6; PR, n=3; PD, n=3). Prior to allo-HCT, eight patients received ≤2 and four patients 3-4 INO cycles. Sinusoidal obstruction syndrome was reported in three patients, including one after transplant. Allo-HCT evaluated as a time-dependent variable had no impact on OS. INO seems to be effective as debulking strategy in r/r-ALL with EMD. However, INO followed by allo-HCT seems not to be effective in maintaining long term disease control.
INTRODUCTION

Historically, 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 blinatumomab or inotuzumab ozogamicin (INO) 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/CR with incomplete hematological recovery (CRi) in 80.7% versus 29.4% of the patients (P<0.001).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 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.\(^1\) The most frequent grade 3 or higher non-hematologic adverse events after INO were liver-related. Veno-occlusive liver disease (VOD) / sinusoidal obstruction syndrome (SOS) of any grade occurred in 15 patients (11%), who received INO and in one patient (1%) after SoC therapy. In addition, 10 of 48 (21%) patients, who underwent an allo-HCT after INO treatment, developed VOD after transplantation; three of these 10 patients had had received a second transplant.\(^1\)

Taken together, deep remissions with MRD negative status can be achieved with INO treatment in patients with r/r ALL. However, the safety and efficacy of INO treatment in patients with r/r ALL and extramedullary disease (EMD) is currently unclear. Patients with central nervous system (CNS) infiltration and/or isolated EMD were excluded from the phase III randomized INO-VATE trial.\(^1\) Of note, extramedullary relapses following blinatumomab exposure in r/r ALL patients are common (up to 40%).\(^18,19\)

EMD in r/r B-ALL is characterized by dismal outcome with no accepted standard therapeutic approaches.\(^1\) The objectives of our study were to characterize a series of adult r/r B-ALL patients with EMD and evaluate outcome after treatment with INO.

**Methods**

Information on 31 adult patients (median age, 31 years; range, 19-81 years) with histologically confirmed r/r B-ALL and EMD, who were treated with INO between 2015 and 2021 within a compassionate use program (n=7) or in-label after approval by the Food & Drug Administration (FDA) or the European Medical Agency (EMA) (n=24) was collected from six institutions in the US and Europe. All 31 patients were
CD22 positive at relapse/progressive disease. Three (10%) of the 31 patients were previously treated with tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia and progressed to *BCR-ABL* positive blast cell crisis of B-lymphoid lineage. Bone marrow evaluation and immunophenotyping by flow cytometry revealed B-ALL in all three patients. The 31 patients were heavily pretreated receiving intensive chemotherapy +/- TKI, as well as blinatumomab in 14, and local irradiation in five patients, respectively. In addition, prior allo-HCT was performed in 18 patients (first line or at relapse, n=9, each).

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 ALL patients with EMD. 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. Data collection and analyses were approved by the Institutional Review Boards of the participating centers.

**Treatment**

INO was dosed at 0.8 mg/m² body surface area (BSA) and applied as a continuous 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=19; 3-4 cycles, n=7; 5-6 cycles, n=5) were administered according to the previously approved
regimen. The three patients with *BCR-ABL* positive blast cell crisis of B-lymphoid lineage received TKI in addition to INO. EMD response assessment was performed by computed tomography (CT) or positron emission tomography-computed tomography (PET-CT). VOD/SOS was assessed according to previously defined clinical criteria and diagnosed by the treating investigator.\(^{15}\)

**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. The median follow-up time was computed using the reverse Kaplan-Meier estimate.\(^{21}\) The Kaplan-Meier method was used to estimate the distribution of RFS and OS.\(^{22}\) OS was calculated from start of INO treatment until last follow-up or death. RFS was calculated from achievement of CR after start of INO treatment until last follow-up or relapse. Confidence interval (CI) estimation for survival curves was based on the cumulative hazard function using Greenwood’s formula for variance estimation. Logrank tests were employed to compare survival curves between groups. The effect of allo-HCT on OS as a time-dependent intervening event was tested by using the Mantel-Byar method\(^{23}\) for univariable and Andersen-Gill model for multivariable analyses.\(^{24}\) The method of Simon and Makuch was used to estimate survival distributions with respect to time-dependent interventions.\(^{25}\) The individuals at risk were initially all represented in the INO therapy group. If patients received an allo-HCT, they were censored at this time point in the INO therapy group and further followed up within the allo-HCT group. All statistical analyses were performed with
the statistical software environment R, version 3.3.1, using the R packages prodlim, version 1.5.7, and survival, version 2.39-5.26.

RESULTS

Patient characteristics

At the time of r/r ALL with EMD, median white blood cell and platelet counts were 5.9/nl (range, 0.04-36/nl) and 110.5/nl (range, 6-337/nl), respectively. Fifteen patients (48%) were female; ECOG was ≤ 2 in 29 patients and 3 in two patients (Table 1). Overall, patients had in median 2 EMD manifestations (range, 1-9). Localization of EMD is shown in Table 2. In addition to EMD, n=16 (52%) patients had a relapse in bone marrow.

Genetics

Cytogenetic analysis at the time of r/r ALL with EMD was available in 13 (42%) patients, of whom six patients had a bone marrow relapse as well. Of those, six patients had a normal karyotype, four were complex (≥3 abnormalities), two patients displayed a t(9;22)(q34;q11) and one had an additional X-chromosome. In one patient clonal evolution to a complex karyotype was detected.

Response

Seven (23%) of the 31 patients had no response assessment after the first induction cycle including one patient who died at day 11 of the first INO cycle due to cerebral hemorrhage. Complete remission assessed by PET-CT (CR; including EMD and
hematological/bone marrow CR) after the first INO cycle was achieved in 10 of 24 assessed patients (42%), nine patients (37.5%) had a partial remission (PR), two (8%) had stable disease (SD) and three (12.5%) showed resistant/progressive disease (RD/PD). After 2 INO cycles, CR was achieved in 17 of 31 patients (55%), PR in nine (29%); one patient (3%) experienced early death and four patients with SD+RD/PD did not receive further INO treatment (13%). Interestingly, only two patients with PR after the first cycle achieved a CR after the second INO cycle, whereas the other seven patients with PR after the first cycle maintained PR.

Patients, who achieved at least a PR after two INO cycles and did not proceed to allo-HCT, could continue with INO up to six cycles.

**Survival**

Median follow-up was 29 months (95%-CI, 21 months - not reached) and median overall survival (OS) 12.8 months (95%-CI, 9.9-16.2 months; Figure 1). One-year and 2-years OS and RFS rates were 53% (95%-CI, 37-76%) and 47% (95%-CI, 25-88%) as well as 18% (95%-CI, 8-43%) and 23% (95%-CI, 7-75%), respectively (Figure 2). In Cox regression analysis age as a continuous variable had no impact on OS (P=0.83). This was also true when using 60 years as cut-off (P=0.2). Twelve patients went on to allo-HCT (CR, n=6; PR, n=3; PD, n=3). Prior to allo-HCT, eight patients received ≤ 2 and four patients 3-4 INO cycles. The influence of allo-HCT assessed as a time-dependent covariable as postremission therapy on OS is illustrated by a Simon Makuch plot (Figure 3). The Mantel-Byar test revealed no impact on OS (P=0.19) for patients proceeding to allo-HCT as compared to consolidation with INO.

In a multivariable Andersen-Gill model including prior allo-HCT before INO treatment,
age at initial diagnosis and allo-HCT after INO as a time-dependent variable no significant impact on OS for any of these variables was detected.

In patients achieving a CR after INO treatment (n=17) median OS was 16.2 months. There was no difference on OS (P=0.08) or RFS (P=0.2) if patients had EMD manifestations only as compared to EMD and bone marrow involvement.

In patients with CR/PR after INO treatment, relapse occurred in 10 of 26 patients (38%; after allo-HCT, n=3); of those, all except one succumbed to their disease. Two patients died in remission (sepsis, VOD/SOS/multi-organ failure, n=1; each); both had received a prior allo-HCT before INO treatment. One patient experienced a molecular relapse, which could be successfully treated with INO again. Ten patients are still in CR (n=9) or PR (n=1), including the patient with prior molecular relapse and INO re-exposure.

Our cohort included also three patients with CNS involvement. The first patient initially developed CNS relapse with positive cytology, but eventually progressed with an epidural mass treated with INO and ponatinib. This patient developed VOD after three INO cycles. Thus, all treatment was held. The cerebrospinal fluid (CSF) remains intermittently positive for ALL (treated with intrathecal chemotherapy), but the peripheral blood remains negative and the epidural mass has not recurred. The second patient was treated with 6x intrathecal methotrexate/cytarabine/dexamethasone. The CSF was negative after the second cycle and remained negative thereafter. Additionally, the patient received four INO cycles and achieved CR without measurable residual disease after the second INO cycle. The patient went on to allo-HCT, but relapsed 3.5 months later and died 8.2 months after relapse.
Finally, in the last patient, CNS relapse was not confirmed (both CSF evaluation and magnetic resonance imaging were equivocal), but suspected due to diplopia, that improved after high dose methotrexate (given before INO). The patient was then switched to six INO cycles and achieved CR by PET-CT after three INO cycles. Unfortunately, the patient presented with systemic (blood/marrow/extramedullary) relapse 1.5 months later. CSF at that time was negative and there were additionally no suggestive CNS symptoms (no recurrence of diplopia or other neurologic deficits). Unfortunately, the patient passed away 13 days after relapse due to rapidly progressive disease.

**VOD/SOS**

Up to 4 INO cycles were administered in patients as bridge to transplant (≤ 2 cycles, n=9; 3-4 cycles, n=3). Overall, VOD/SOS was reported in three (10%) patients, including one (8%) of 12 patients after transplant. The first patient experienced VOD at the first day of the third INO cycle prior to allo-HCT, but continued to transplantation after resolution and is in an ongoing CR. The second patient developed VOD after 3 INO cycles and therefore stopped INO treatment. This patient did not proceed to allo-SCT and is in CR 30.7 months after start of INO treatment. The third patient received 2 INO cycles prior to haplo-identical allo-HCT with a conditioning regimen consisting of treosulfan/fludarabine/thiotepa. This patient developed VOD after transplant and died 13.1 months after allo-HCT due to multi-organ failure and VOD.

**DISCUSSION**
EMD is described in 20% of patients with ALL, and it is more common in patients with T-cell phenotype, as well as in patients with lymphoblastic lymphoma presentation, without bone marrow involvement.²⁷ EMD may involve different sites, as observed in our series.²⁸,²⁹ The role of INO as treatment for patients with r/r ALL and EMD has largely not been studied. The randomized phase III INO-VATE trial included only seven r/r ALL patients with EMD and INO treatment as well as five patients treated with standard of care chemotherapy.³⁰ Among patients with baseline EMD, five of seven (71%) in the InO arm and two of five (40%) in the SC arm achieved CR/CRi, which included resolution of EMD.³⁰ Consistent with previous reports on the effectiveness of INO in patients with EMD, we observed a high CR rate of 55% after INO treatment in patients with r/r ALL and EMD.³⁰-³² There was no difference based on the presence or absence of concurrent medullary disease. Additionally, the median OS of 12.8 months in our cohort of heavily pretreated patients compares favorably to the less heavily pre-treated patients enrolled in the INO-VATE trial (7.7 months), although the number of patients with EMD in the aforementioned trial was very low limiting comparison.³¹ The high response rate of ALL with EMD treated with INO may be an advantage of INO treatment since the presence or history of EMD may predict poor responses to other therapies, specifically blinatumomab.¹⁹ In a retrospective cohort study of 65 patients with r/r ALL, a high leukemia burden defined as bone marrow blast cells >50% (OR = 0.24; P = 0.02) as well as presence of (OR = 0.19; P = 0.05) or history of EMD (OR = 0.23; P = 0.005) were associated with lower response to blinatumomab.¹⁹ It remains unknown whether increasing the dose of blinatumomab for ALL would be able to overcome this resistance (and tolerable), since for non-Hodgkin lymphomas a higher dose has been studied and resulted in reasonable results.³³ In contrast to blinatumomab,³⁴ only few cases of
CD22 antigen loss have been described so far. In our cohort, we did not observe any CD22 antigen loss. In the INO-VATE trial, the inclusion of a small group of CD22 negative or CD22 low expression cases was reported. Interestingly, three of five of these patients showed a response to INO treatment. In addition, response in a CD22 negative patient was described in a case report as well. Thus, INO might be active in CD22 negative patients and/or those with very dim CD22 expression, but this issue remains to be elucidated in larger studies. Recent data from the INO-VATE trial suggests that patients with high (≥90%) CD22 expression levels had a higher CR rate (42.1% (n=45/107) vs 20% (n=7/35)) for patients with CD22 positivity ≥90% as compared to those with <90%, respectively. According to the EMA label, the CD22 expression needs to be above 0%, including also patients with very dim CD22 expression levels. For the US, no particular CD22 expression was included by the FDA.

Moreover, lineage switch mechanism (myeloid conversion), described mostly in CAR-T cell therapy, does not seem to involve CD22 expression: the antigen is maintained on the intermediate phenotype relapses, suggesting that simultaneous pressure on CD19 and CD22 might avoid this resistance mechanism.

Increased INO exposure has been associated with an increased risk of VOD/SOS following allo-HCT, leading to the recommendation that patients being bridged to allo-HCT be treated with two or fewer cycles of INO (three cycles if necessary to achieve an MRD-negative CR/CRi). In our cohort, VOD/SOS was reported in three patients only, including one after allo-HCT, although up to four INO cycles were administered prior to allo-HCT. These data compare favorably to previously reported data.
Our analysis has several limitations. Since this is a retrospective, non-randomized cohort analysis no direct comparison to outcome of r/r ALL with EMD after standard-of-care chemotherapy treatment was feasible. However, since all patients were heavily pretreated with intensive chemotherapy including prior allo-HCT in 58% of the patients, we believe that standard-of-care chemotherapy would have failed to induce a remission. The overall prognosis remains poor even if patients could be successfully bridged to allo-HCT, strongly arguing for alternate consolidation approaches, such as chimeric antigen receptor T-cells or advanced bi-specific antibodies. Nevertheless, the ability of INO to be given in an outpatient setting with few toxicities may continue to make it a value tool in the treatment of B-ALL.

**Conclusions:** This outcome analysis demonstrates that treatment with INO is an effective and promising approach in r/r-ALL patients with EMD. The CD22 status should be routinely assessed at diagnosis and r/r B-ALL patients, in order to better evaluate the indication for INO treatment. However, allo-HCT alone seems not to be effective in maintaining disease control. Thus, chimeric antigen receptor T-cells or advanced bi-specific antibodies as consolidation therapy should be evaluated in the future.
REFERENCES


**Table 1:** Patient characteristics at the time-point of relapsed/refractory acute lymphoblastic leukemia and extramedullary disease

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Abbreviations: BM, bone marrow; ECOG, eastern cooperative oncology group; WBC, white blood cell count.
KAYSER et al. Outcome of relapsed/refractory B-ALL with extramedullary disease after Inotuzumab Ozogamicin
Table 2: Localization of extramedullary disease*

<table>
<thead>
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<td>Gastrointestinal organs</td>
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*Overall, patients had in median 2 extramedullary disease manifestations (range, 1-9). Each localization of extramedullary disease was counted separately; thus, the total number does not add up to the total number of patients.
**Figure 1**: Overall survival of relapsed/refractory patients with B-acute lymphoblastic leukemia and extramedullary disease after treatment with Inotuzumab ozogamicin. Green and red dotted lines indicate upper and lower 95% confidence interval.

**Figure 2**: Relapse-free survival of patients attaining complete remission. Green and red dotted lines indicate upper and lower 95% confidence interval.

**Figure 3**: Simon Makuch plot illustrating the influence of allogeneic hematopoietic stem cell transplantation on overall survival.

**Figure 4**: Whole body 18-fluorodeoxyglucose positron emission tomography-computed tomography. Panel A: before start of INO treatment; Panel B: after one INO cycle, showing partial remission.

**Figure 5**: Contrast-enhanced imaging by positron emission tomography-computed tomography (axial slice). Panel A: before start of INO treatment; Panel B: after one INO cycle, showing complete remission.
Figure 2

The graph illustrates the relapse-free survival (%) over time (months). The x-axis represents time in months, ranging from 0 to 24, and the y-axis represents relapse-free survival in percentages, ranging from 0 to 100. The numbers at risk at each time period are as follows: 31, 27, 22, 19, 13, 10, 5, 4, and 3.
Figure 3

The Kaplan-Meier survival curve shows the percentage of survival over time. The red line represents the Allo-HCT group with 12 patients, and the black line represents the control group.

Numbers at risk:

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