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【 CASE REPORT 】

# Clinical Significance of Inotuzumab Ozogamicin in Non-transplant Patients with Relapsed Acute Lymphoblastic Leukemia: A Report of Four Cases

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**Abstract:**
Relapsed acute lymphoblastic leukemia (ALL) has a poor prognosis. Inotuzumab Ozogamicin (InO) is a novel therapeutic drug for the treatment of relapsed ALL. InO has received attention as a bridging therapy before transplantation due to its high complete remission (CR) rate. However, the significance of InO in non-transplant patients remains unclear. We retrospectively evaluated four non-transplant patients treated with InO. All cases achieved CR after receiving at least two cycles of InO. Three of the four cases survived for more than 11 months without relapse. Moreover, all patients received InO as outpatients, because the adverse events were well-controlled. InO therefore appears to be a beneficial treatment even for non-transplant patients.

**Key words:** Inotuzumab Ozogamicin, acute lymphoblastic leukemia, relapsed/refractory

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## Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by the proliferation of lymphoid progenitor cells in bone marrow. The median overall survival (OS) and the 5-year OS rate of relapsed or refractory (RR)-ALL have been reported to be 6 months and <10%, respectively (1, 2). The only curative treatment option following relapse after achieving a second complete remission (CR) is allogeneic hematopoietic stem cell transplantation (HSCT). However, the CR rate of first salvage chemotherapy is reported to only be around 40% (1, 2).

Inotuzumab Ozogamicin (InO), a novel therapeutic drug for RR-ALL, was approved by the United States Food and Drug Administration in 2017 and in Japan in 2018. InO is an anti-CD22 monoclonal antibody (Inotuzumab) conjugated with calicheamicins, which belongs to the class of antibiotics with cytotoxic properties, via chemical linkers. CD22 is expressed in more than 90% of all patients with ALL (3). The mechanism of action of InO is as follows: InO binds to CD22 on the surface of ALL cells. It is then internalized and forms endosomes, which fuse with lysosomes. The linkers are degraded in the lysosomes due to the acidic environment. The released calicheamicin binds to the minor groove of DNA, which induces double strand cleavage and subsequent apoptosis (4).

InO has drastically improved the treatment of RR-ALL. A randomized phase III clinical trial, the INO-VATE study, which included 55 Asian patients, showed that the CR/CRi (CR with incomplete hematologic recovery) rate was significantly higher than the standard of care (SoC) with intensive chemotherapy including FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor), MXN/Ara-C (mitoxantrone and cytarabine), and HIDAC (high-dose cytarabine) (80.7% vs. 29.4%) (5). However, InO was not associated with a prolonged OS (7.7 months vs. 6.2 months) (6, 7). Therefore, InO has generally attracted attention as a bridging therapy to HSCT.

The clinical significance of InO in patients with RR-ALL who are not eligible for HSCT remains unclear. In the present study, we focused on non-transplant cases with relapsed ALL and evaluated the clinical efficacy of InO in these patients.

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**Table.** **Patients Characteristics.**

| Case No. | Age | Gender | Ph | Status of relapse | Blasts in PB (/μL) (%) | Blasts in BM (%) | Chromosome |
|---|---|---|---|---|---|---|---|
| 1 | 52 | F | + | first relapse | 281,725 (95.5%) | N. D. | Complex karyotype including t(9;22)* |
| 2 | 55 | F | - | first relapse | 187,180 (98%) | 97.6 | Complex karyotype** |
| 3 | 72 | F | - | third relapse | 98 (2.5%) | 93.2 | 46, XX |
| 4 | 77 | F | - | first relapse with tumor formation | 0 | 65.4 | 46, XX |

F: female, Ph: Philadelphia chromosome, InO: Inotuzumab Ozogamicin, CR: complete remission, PB:peripheral blood, BM: bone marrow, N.D.: not determined

*46, XX, der(3)t(3;22)(q21;q13), add(9)(p13), der(9)t(9;22)(q34;q11.2)t(3;22), der(22)t(9;22)[11]/46, idem, t(X;11)(p22.1;p15)[2]/46, idem, t(2;11)(p23;p13)[1]/46, idem, t(12;12)(p13;p22)[5]/46, idem, t(12;19)(p11.2;p13)[1]

**47, XX,+X, der(18)t(1;18)(q21;q21)[12]/47, XX,+der(X)t(X;1)(q28;q21)[3]/47, XX,+X, der(6)t(1;6)(q21;q21)[2]/47, XX,+X, der(14)t(1;14)(q21;p11.2)[2]/47, XX,+X, der(18)t(1;18)(q21;q23)[1]

## Case Report

### Patient characteristics

We retrospectively evaluated the clinical features and therapeutic responses of four cases of relapsed ALL who were treated with InO at our institution. The characteristics of the four patients are shown in Table. Cases 1 and 2 were in their fifties, which are generally transplantable ages, although they refused HSCT because of psychological problems. Cases 3 and 4 were not eligible for HSCT because of their older age.

### Clinical courses

Case 1 (52-year-old female) had Philadelphia (Ph)-positive ALL with T315I mutation that first relapsed during the third cycle of consolidation therapy (Figure A). Cytoreduction was performed by combination chemotherapy using vincristine (VCR), doxorubicin (DOX), cyclophosphamide (CPA), and steroids, because absolute peripheral blood blast counts (ABC) were extremely high. CR with 5-log reduction of Breakpoint cluster region-Abelson (BCR/ABL) transcripts was achieved with one cycle of InO. After the second cycle of InO, since the patient's aspartate aminotransferase (AST) levels increased to more than 2.5 times the upper limit of normal (ULN), InO was withdrawn temporarily according to the instructions of the package insert. A second relapse was observed during the third cycle of InO. Hence, the treatment was switched to ponatinib. She died of disease progression 7 months after the initiation of InO. The duration of CR (DuCR) was 2 months.

In Case 2 (55-year-old female), ALL relapsed 12 years after the initial diagnosis (Figure B). Steroids were administered for cytoreduction because her ABC was extremely high. CR was achieved with one cycle of InO. Moreover, no measurable residual disease (MRD) was detected in bone marrow by conventional flow cytometry. InO was discontinued after the fourth cycle due to increased AST and Bil levels, because these adverse events (AEs) were grade 2 according to the Common Terminology Criteria for Adverse Events. Although she has survived for 15 months, she had relapsed 13 months after achievement of CR with InO. Currently, she is enrolled in the clinical trial of Chimeric Antigen Receptor (CAR) T-cell therapy.

In Case 3 (72-year-old female), Ph-negative ALL relapsed for a third time 8 years after the initial diagnosis (Figure C). CR was achieved with two cycles of InO, and MRD was not detected in bone marrow by conventional flow cytometry. However, she temporarily discontinued drug treatment due to grade 3 thrombocytopenia and an elevation of the AST and Bil levels to over 2.5 times the ULN after the third and fourth cycles of InO. The liver damage disappeared and the platelet counts recovered to 50,000/μL or more, which is the starting criteria for next cycle with InO withdrawal. The fifth cycle of InO was then started, however, both liver damage and thrombocytopenia appeared again. InO was thus discontinued during the fifth cycle, because she was considered to be intolerant to InO. She has survived for 13 months without relapse. Her DuCR is 11 months.

In Case 4 (77-year-old female), Ph-negative ALL relapsed with tumor formation at the uterine cervix 6 years after the initial diagnosis (Figure D). CR was achieved and the tumor was reduced with a CHOP-like chemotherapy regimen, although MRD was detected in bone marrow by conventional flow cytometry. MRD became negative with the subsequent cycle of InO. The treatment was repeated up to 6 cycles. Grade 1 AEs, in the form of increased Bil and AST levels, were observed after the sixth cycle of InO. She has since been observed without treatment and has survived for 14 months without relapse. Her DuCR is 13 months.

## Discussion

The treatment strategies for RR-ALL vary depending on whether the patient is eligible for HSCT or not. In salvage chemotherapy for transplant patients, the CR rate, MRD negativity rate, and lack of impact on HSCT are important. The INO-VATE study showed that more patients treated with InO proceeded directly to HSCT compared with pa-

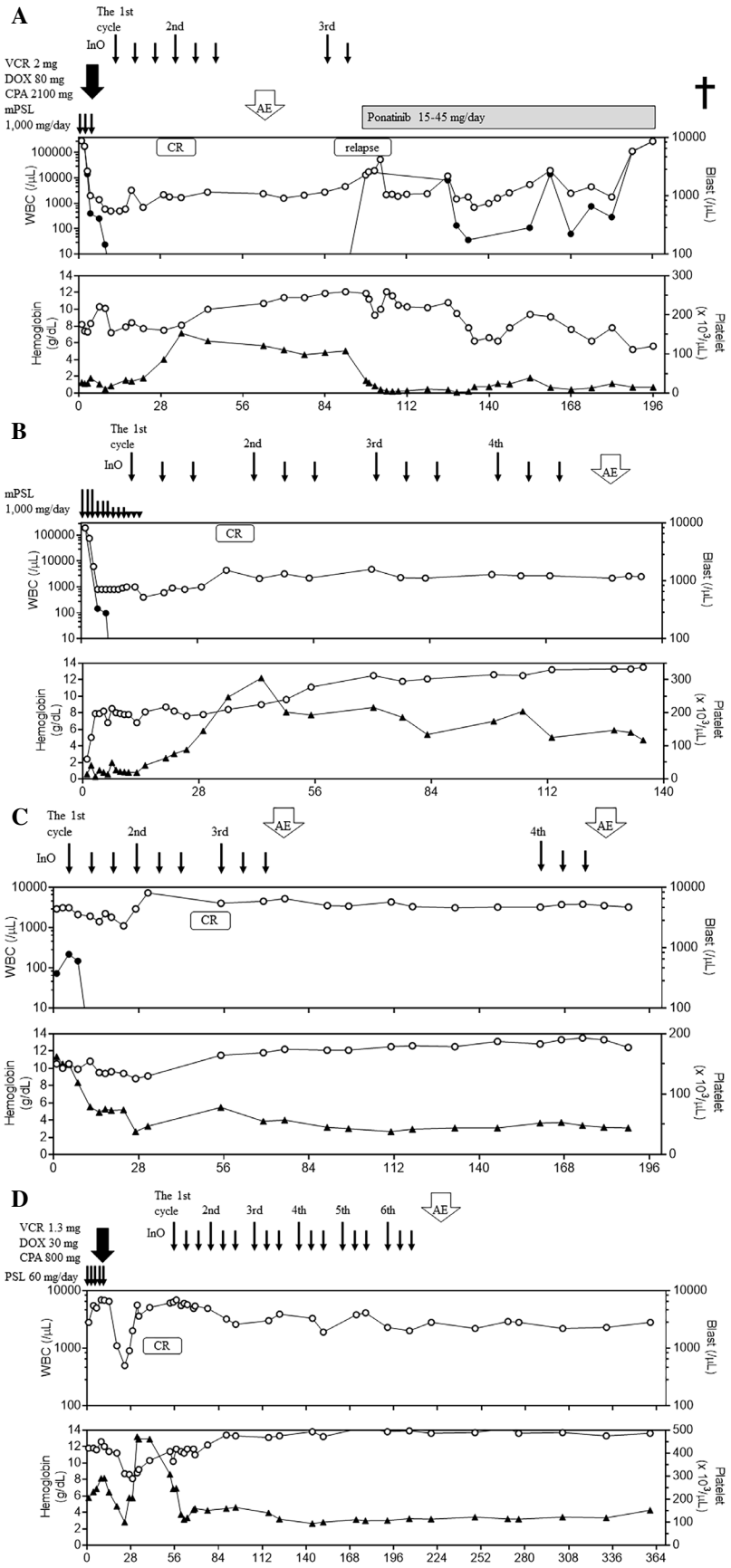


**Figure.** **The clinical course of Cases 1, 2, 3, and 4. The upper panel shows WBCs (open circles) and blasts in peripheral blood (closed circles). The lower panel shows hemoglobin (open circles) and platelets (closed triangles) in peripheral blood. VCR: vincristine, DOX: doxorubicin, PSL: prednisolone, mPSL: methylprednisolone, WBC: white blood cell, InO: Inotuzumab Ozogamicin, CR: complete remission, AE: adverse event**

tients treated with the SoC (41% vs. 11%). It was thought that the high rates of CR and MRD negativity (78.1%) with InO enable the patient to proceed to HSCT (7). However, there is reportedly no significant difference in the OS between patients treated with InO versus SoC. Therefore, InO is positioned as a bridging therapy to HSCT.

On the other hand, a prolonged duration of remission and the maintenance of the patients' QOL are desirable for non-transplant patients on salvage chemotherapy. The duration of remission with InO was reported to be longer than that with the SoC (6.4 months vs. 3.1 months) (8). In the INO-VATE study, patient-reported outcomes were assessed using the EORTC-QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire), EQ-5D Index (EuroQoL 5 Dimensions Questionnaire), and EQ-VAS (visual analog scale). In that study, patients treated with InO were reported to have better QOL than those treated with SoC (9). In the present study, three of the four cases had long-term survival with CR, and AEs were well-controlled.

A previous multivariate analysis suggested that chromosomal abnormalities, including complex karyotypes and the Ph chromosome, more than one salvage chemotherapy, and ABC >1,000/μL were independent poor prognostic factors for survival with InO treatment. Patients with all of these factors died within half a year, patients with two of the three factors died within a year, 20% of patients with one factor survived for 18 months, and all patients without these factors survived for 36 months (10). In the present study, Cases 1 and 2 had two of these prognostic factors, Case 3 had one, and Case 4 had none. Although an ALL tumor was determined in Case 4, a previous case report showed two cases with ALL tumors, which were responsive to InO (11). Therefore, Case 4 might be expected to have long-term survival. ALL cases that had relapsed three or more times were not included in the INO-VATE study. Case 3, with three relapses of ALL, suggests that InO is also effective in ALL cases that have relapsed three or more times.

Blinatumomab (Blina), a bispecific T cell-engager antibody against CD19/CD3, is also a treatment option for RR-ALL. However, there have been no head-to-head studies comparing InO and Blina. Indirect treatment comparisons were conducted to compare the relative efficacy of these two treatments using data from the INO-VATE study and TOWER study about Blina (12). The study revealed a statistically significantly higher CR/CRi rate of InO and a tendency favoring InO for event-free survival, although there were no differences in OS. Interestingly, the CR/CRi rate of InO did not depend on the tumor volume, unlike Blina (7). Moreover, QOL with Blina might be compromised by the need for continuous infusion of Blina for 28 days. On the other hand, once-weekly administration of InO allows for ambulatory treatment. In fact, all our cases received InO as ambulatory treatment after achieving CR. This advantage of InO is considered to be a significant benefit that improves QOL in non-transplant patients. Another treatment option for RR-ALL is Tisagenlecleucel, which is anti-CD19 CAR T-cell therapy. It has been reported that CD19 disappeared in 8% of patients who had a relapse after Blina (13). Although the efficacy of CAR T-cell therapy has been reported to be independent of the expression level of CD19, prior treatment with Blina showed a higher rate of failure to achieve MRD-negative CR by subsequent CAR T-cell therapy (14). Hence, InO might be more appropriate than Blina as a prior treatment of CAR T-cell therapy.

In conclusion, the present study suggested that InO treatment might be beneficial for the treatment of some RR-ALL patients who are not suitable candidates for HSCT.

**The authors state that they have no Conflict of Interest (COI).**

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