Received: 6 November 2023 | Revised: 23 November 2023 | Accepted: 24 November 2023

DOI: 10.1002/ccr3.8289

CASE REPORT

Clinical Case Reports Open Access WILEY

Preemptive inotuzumab ozogamicin eradicated measurable residual disease in Ph-negative acute lymphoblastic leukemia relapsed post CD19 CART therapy

Si-Man Huang[1,2,3] | **Chao-Ling Wan**[1,2,3] | **Han-Yu Cao**[1,2,3] | **Yan-Yan Li**[1,2,3] | **Chong-Sheng Qian**[1,2,3] | **Hai-Xia Zhou**[1,2,3] | **Ming-Zhu Xu**[1,2,3] | **Xiao-Hui Hu**[1,2,3] | **Lan Dai**[1,2,3] | **Hai-Ping Dai**[1,2,3] | **Sheng-Li Xue**[1,2,3]

[1]National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China

[2]Institute of Blood and Marrow Transplantation, Collaborative Innovation Center of Hematology, Soochow University, Suzhou, China

[3]Collaborative Innovation Center of Hematology, Soochow University, Suzhou, China

Correspondence
Hai-Ping Dai and Sheng-Li Xue, National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, No. 188, Shizi Street, Suzhou 215006, China.
Email: daihaiping8@126.com and slxue@suda.edu.cn

Funding information
Gusu Key Medical Talent Program, Grant/Award Number: GSWS2019007; Jiangsu Province "333" Project, Social Development Project of the Science and Technology Department of Jiangsu, Grant/Award Number: BE2021649; Jiangsu Province Natural Science Foundation of China, Grant/Award Number: BK20221235; National Key Research and Development Program of China, Grant/Award Number: 2022YFC2502703; National Natural Science Foundation of China, Grant/Award Number: 81970138 and 82270165; Translational Research Grant of NCRCH, Grant/Award Number: 2020ZKMB05

Key Clinical Message

There are no reports of application of inotuzumab ozogamicin (InO) for the treatment of MRD in r/r B-ALL. We firstly report the efficacy of InO for a patient experienced morphological relapse after HSCT and molecular relapse after CART therapy.

KEYWORDS

B-ALL, CD22, inotuzumab ozogamicin, MRD positive, relapsed and refractory

Si-Man Huang, Chao-Ling Wan and Han-Yu Cao contributed equally as first author.

Hai-Ping Dai and Sheng-Li Xue contributed equally as corresponding author.

1 | INTRODUCTION

The prognosis of adult relapse or refractory B-cell acute lymphoblastic leukemia (r/r B-ALL) is dismal, with a complete remission rate of approximately 18%–44% if receiving salvage chemotherapy.[1] In recent years, immunotherapy represented by blinatumomab, inotuzumab ozogamicin (InO), and chimeric antigen T-cell (CART) therapy has demonstrated profound efficacy in r/r B-ALL.[3–5] However, those who have persistent positive measurable residual disease (MRD) still remain a high risk of relapse and poor outcome.[2] So far, blinatumomab is the only approved immunotherapy for the treatment of MRD in r/r ALL.[4] CD22 is detected to be expressed in more than 90% of B-ALL patients, indicating that CD22 is an ideal therapeutic target for B-ALL.[6] InO is an antibody-drug conjugate comprising a humanized anti-CD22 monoclonal antibody conjugate to calicheamicin. According to the INO-VATE study, significantly higher rate of complete remission was observed in r/r B-ALL patients who received InO monotherapy compared with traditional chemotherapy (73.8% vs. 30.9%, $p < 0.0001$) This encouraging data lead to the approvement of InO for the treatment of r/r B-ALL by the US Food and Drug Administration in 2017.[3] Hitherto, the application of InO in the treatment of MRD has not been reported.

2 | CASE HISTORY

A 17-year-old female presented with epistaxis and bleeding gums in February 2019. Complete blood cell count showed white blood cells 26.98×10^9/L, hemoglobin 79 g/L, and platelets 12×10^9/L. Physical examination did not reveal splenomegaly or enlarged lymph nodes. A differential count found 91% blasts. Flow cytometry (FCM) analysis revealed 31.5% of blasts, which were positive for CD10, CD19, CD79a, and HLA-DR. The diagnosis of B-ALL was confirmed. Cytogenetics was normal. No fusion genes or mutations were detected with polymerase chain reaction and targeted next-generation sequencing. Complete remission (CR) was not achieved after induction therapy with the Hyper-CVAD regimen (cyclophosphamide 300 mg/m^2 every 12 h days 1 to 3, vincristine 1.4 mg/m^2 day 4 and day 11, doxorubicin 50 mg/m^2 day 4 and dexamethasone 40 mg days 1 to 4, days 11 to 14)[7] (11.5% blasts in morphology). After reinduction with idarubicin (10 mg, day 1), pegasparagase (3750 U, day 1), and dexamethasone (15 mg, days 1 to 14), she achieved CR but measurable residual disease (MRD, 1.6%) was detected by FCM. This was followed by consolidation therapy, including 1 cycle of high-dose methotrexate plus vincristine and dexamethasone (methotrexate 2 g/m^2 day 1, vincristine 1.4 mg/m^2 day 1, dexamethasone 15 mg, days 1 to 7), and 1 cycle of high-dose cytarabine (2 g/m^2, every 12 h, days 1 to 3). To prevent central nervous system infiltration, intrathecal chemotherapy with methotrexate was used. However, MRD was consistently detected in bone marrow specimens. Though she had no unfavorable genetic aberrations at diagnosis, the persistence of MRD supported the risk classification of high-risk group. As neither blinatumomab nor InO were approved for marketing in China in 2019, she received haploidentical hematopoietic stem cell transplantation (HSCT) from her father in August 2019. The FCM MRD prior to HSCT was 1.47%. The conditioning regimen was modified BuCy.[8] Cyclosporin, mycophenolate mofetil, and methotrexate were used to prevent graft versus host disease(GVHD). She did not suffer from acute or chronic GVHD, and immunosupressors were tapered off and stopped in 6 months post transplantation. Unfortunately, a hematologic relapse was detected 23 months post-transplant (July 2021). She was then enrolled in a clinical trial (NCT04825496) and received autologous anti-CD19 CART therapy (dose: 1×10^6/kg). At the day 28 evaluation after CAR T-cell infusion, the patient achieved a MRD negative remission. She developed grade 2 cytokine release syndrome presented with fever and hypotension, which was relieved with symptomatic treatment. No immune effector cell-associated neurotoxicity syndrome (ICANS) was observed (Figure 1A). The persistence of CAR T cells was only detected within a month following CART therapy (Figure 1B). At the regular follow-up in August 2022, MRD-positive relapse was detected (3% of blasts by morphology, which were positive for CD10, CD19, CD22, and CD38, and negative for CD20). Expression of CD22 was detected in 63.74% of the blasts. InO was selected for the treatment of MRD. InO was applied 3 times: 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15. Ursodeoxycholic acid was administered to prevent the development of liver venoocclusive disease (VOD). She experienced only mild nausea. Grade 1 neutropenia and grade 4 thrombocytopenia were observed, which recovered with supportive care. At day 30 evaluation, no blasts were detected in the BM smear. Surprisingly, the MRD by FCM decreased to 2.68×10^{-5} and CD22 expression was negative (Figure 1C–E). No sinusoidal obstruction syndrome or other adverse effects occurred. Currently, the patient is in remission until follow-up to September 2023. Timeline of the treatments and responses are shown in Figure 1F.

3 | DISCUSSION

Here, we report the application of InO for the treatment of MRD in a patient with r/r ALL who relapsed post allo-HSCT and anti CD19 CART therapy. The adverse effect related to InO therapy is mild and reversible. Our data

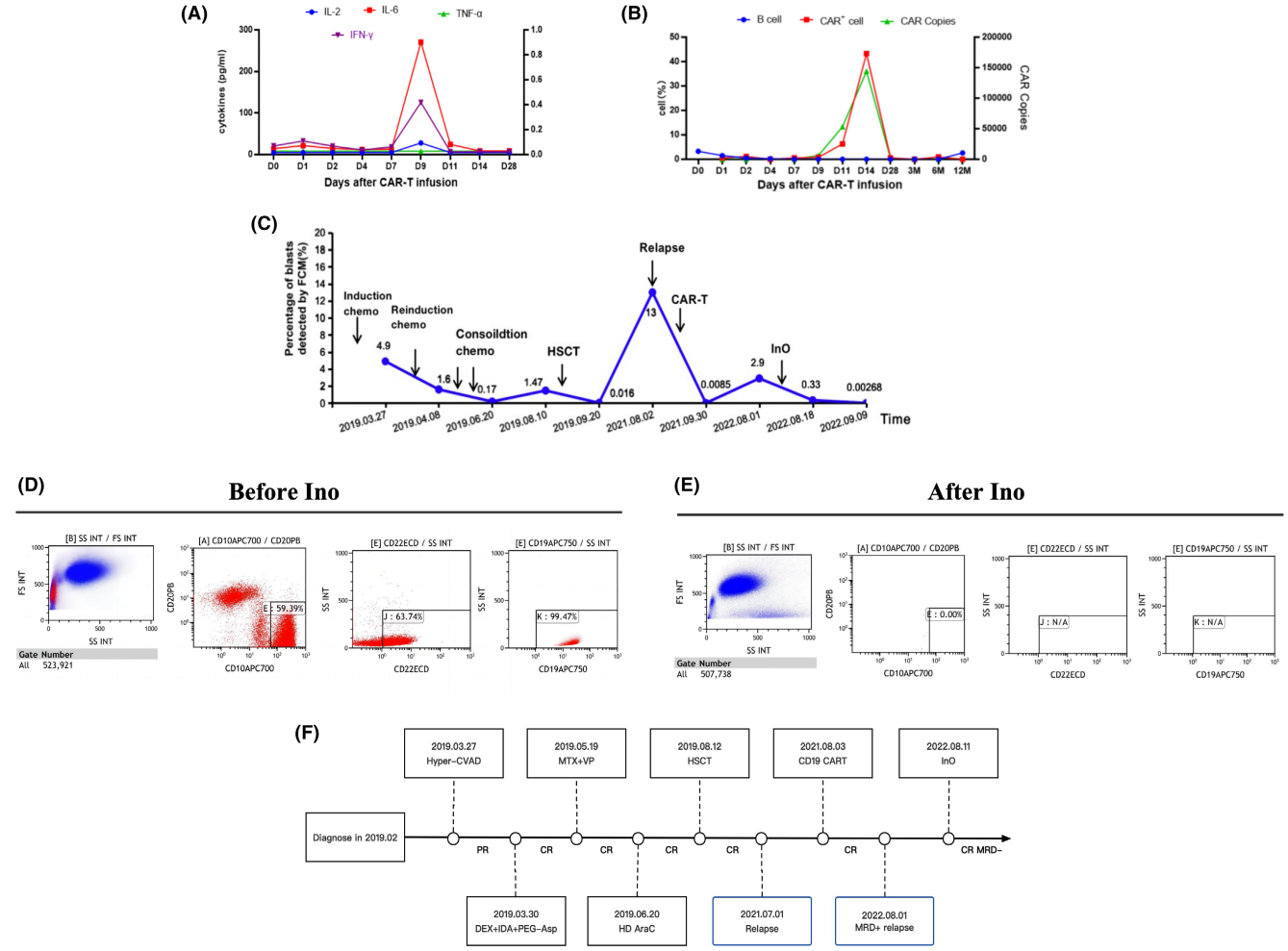

FIGURE 1 (A) Levels of cytokines after CAR T cells infusion. (B) Amplification of CAR T cells detected by qPCR. (C) Change of MRD detected by FCM. (D) FCM analysis before InO. (E) FCM analysis after InO. (F) Timeline of treatments and responses for the patient. Chemo, chemotherapy; CR, complete remission; PR, partial remission; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; DEX+IDA+PFG-Asp, dexamethasone+idarubicin+pegasparagase; MTX, methotrexate; VP, vincristine, dexamethasone, AraC, cytarabine; MRD−, minimal residual disease negative.

provide rationale for the utilization of InO at the scenario of MRD positivity in B-ALL.

Antibody-drug conjugate offers high possibility of achieving remission in r/r B-ALL. InO is a humanized monoclonal antibody which binds CD22 and deliver the conjugated calicheamicin inside the cell after the link is hydrolyzed.[9] The efficacy and safety of InO in patients with r/r Ph-negative B-ALL has been demonstrated. Hagop reported the results of the phase 3 inotuzumab ozogamicin trial (the InO-VATE study), which investigate the tolerability and efficacy of InO in r/r B-ALL.[10] A significantly higher rate of complete remission was observed in InO cohort compared with the standard-therapy group (80.7% vs. 29.4%). A significantly longer progression-free survival (PFS) (5 months vs. 1.8 months, hazard ratio, 0.45) and median overall survival (OS) (7.7 months vs. 6.7 months, hazard ratio, 0.77) were both observed in the InO cohort. Grade 3 or higher thrombocytopenia and febrile neutropenia were significantly lower in the InO cohort than in the standard-therapy cohort (37% vs. 59%; 24% vs. 49%). These results confirmed both efficacy and safety of InO for the treatment of B-ALL. VOD is a unique nonhematologic adverse event associated with InO. The patient in this study did not complicate VOD; hence, our experience supported the use of ursodeoxycholic acid to prevent VOD.

Achievement of MRD negativity associated with improved survival in B-ALL.[2] InO was also efficacious to induce MRD negativity in B-ALL. In the INO-VATE study, 76 of 164 patients receiving InO achieved and remained MRD negativity until the end of follow-up. The survival benefit was more obvious in MRD negative patients. The superior PFS and OS were also demonstrated in the MRD negative patients compared with those in the MRD-positive patients.[11] In a phase 2 trial of InO in children and adolescents with r/r B-ALL, 18 of 27 patients (66.7%) achieved MRD negativity after 1 cycle

of InO treatment. Wiley retrospectively analyzed eight patients who relapsed post-HSCT and received InO followed by donor lymphocyte infusion. 6/8 (75%) patients obtained MRD negative CR after the second cycle of InO.[12] Hence, InO is a preferential option for the treatment of r/r B-ALL.

This patient had persistent MRD prior to HSCT and suffered twice relapses (one hematologic and one molecular relapse) after HSCT, and her prognosis was deemed to be poor. Blasts in the second relapse were positive for CD19, indicating the relapse was caused by loss of CD19 CAR T cells persistence. A second infusion of CD19 CAR T cells was reported to induce CR in only 21% of patients with ALL,[13] so this patient declined another round of CD19 CART. DLI is the conventional preemptive therapy for MRD clearance but carries a high risk of acute GVHD.[14] Blinatumomab is a CD19/CD3 bispecific T-cell engager antibody, which has notable single agent activity in r/r B-ALL. Blinatumomab combined with DLI was reported to salvage a patient with r/r B-ALL from relapse after haplo-HSCT.[15] Blinatumomab and DLI were not chosen for our patient due to concerns about DLI-related GVHD and the inconvenience of blinatumomab requiring continuous infusions. Due to the high CD22 expression (63.74%), low tumor burden and the extended infusion interval of InO, this patient chose InO monotherapy. Overall, our preliminary result showed that InO is effective and safe in eradicating MRD in the setting of multiple relapses after anti-CD19 CART therapy and allo-HSCT. It implied that a double immunotherapy strategy comprising sequential application of CART and ADC-conjugated antibody is feasible and promising for the treatment of R/R B-ALL. Clinical trials applying InO to treat MRD are currently underway. The results of these trials have not been fully disclosed in publications. A prospective clinical study with expanded sample size will provide a basis for the use of InO for MRD eradication and guide the choice of preemptive immunotherapy for r/r B-ALL.

AUTHOR CONTRIBUTIONS

Si-Man Huang: Writing – original draft. **Chao-Ling Wan:** Writing – original draft. **Han-Yu Cao:** Writing – original draft. **Yan-Yan Li:** Project administration. **Chong-Sheng Qian:** Project administration. **Hai-Xia Zhou:** Methodology. **Ming-Zhu Xu:** Project administration. **Xiao-Hui Hu:** Project administration. **Lan Dai:** Formal analysis; methodology. **Hai-Ping Dai:** Formal analysis; writing – review and editing. **Sheng-Li Xue:** Funding acquisition; methodology; writing – review and editing.

FUNDING INFORMATION

This work was supported by the grants from the National Natural Science Foundation of China (Grant Nos. 81970138, 82270165), National Key R&D Program of China (Grant No. 2022YFC2502703), Jiangsu Province Natural Science Foundation of China (Grant No. BK20221235), Translational Research Grant of NCRCH (Grant No. 2020ZKMB05), Jiangsu Province "333" Project, Social Development Project of the Science and Technology Department of Jiangsu (Grant No. BE2021649), and Gusu Key Medical Talent Program (Grant No. GSWS2019007).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data presented in this study are available in this article.

ETHICS STATEMENT

The patient has provided written informed consent for the publication of this case report.

CONSENT

Written informed consent of the patient was obtained for publication.

ORCID

Si-Man Huang https://orcid.org/0000-0002-2131-6608
Han-Yu Cao https://orcid.org/0000-0003-3022-6935
Sheng-Li Xue https://orcid.org/0000-0003-4609-616X

REFERENCES

1. Bassan R, Hoelzer D, Thomas X, et al. Clinician concepts of cure in adult relapsed and refractory Philadelphia-negative B cell precursor acute lymphoblastic leukemia: a Delphi study. *Adv Ther*. 2019;36:870-879.
2. Gökbuget N, Dombret H, Giebel S, et al. Minimal residual disease level predicts outcome in adults with Ph-negative B-precursor acute lymphoblastic leukemia. *Hematology*. 2019;24:337-348.
3. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375:740-753.
4. Topp MS, Gökbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell–engager Blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32:4134-4140.
5. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439-448.
6. Lanza F, Maffini E, Rondoni M, Massari E, Faini AC, Malavasi F. CD22 expression in B-cell acute lymphoblastic leukemia: biological significance and implications for inotuzumab therapy in adults. *Cancers (Basel)*. 2020;12:303.
7. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a

dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*. 2004;101:2788-2801.
8. Huang H, Zhang L, Jiang Y, et al. Modified BuCy is an alternative conditioning regimen for lymphoma patients undergoing autologous stem cell transplantation. *Ann Hematol*. 2019;98(5):1259-1266.
9. Thomas X. Inotuzumab ozogamicin in the treatment of B-cell acute lymphoblastic leukemia. *Expert Opin Investig Drugs*. 2012;21:871-878.
10. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. *Cancer*. 2019;125:2474-2487.
11. Jabbour E, Gökbuget N, Advani A, et al. Impact of minimal residual disease status in patients with relapsed/refractory acute lymphoblastic leukemia treated with inotuzumab ozogamicin in the phase III INO-VATE trial. *Leuk Res*. 2020;88:106283.
12. Papayannidis C, Sartor C, Dominietto A, et al. Inotuzumab ozogamicin and donor lymphocyte infusion is a safe and promising combination in relapsed acute lymphoblastic leukemia after allogeneic stem cell transplant. *Hematol Oncol*. 2021;39:580-583.
13. Gauthier J, Bezerra ED, Hirayama AV, et al. Factors associated with outcomes after a second CD19-targeted CAR T-cell infusion for refractory B-cell malignancies. *Blood*. 2021;137:323-335.
14. Loren AW, Porter DL. Donor leukocyte infusions for the treatment of relapsed acute leukemia after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2008;41:483-493.
15. Chan WYK, Lee PPW, Cheuk DKL, et al. Blinatumomab with donor lymphocyte infusions post-haploidentical hematopoietic stem cell transplantation as salvage therapy for relapsed refractory acute lymphoblastic leukemia post chimeric antigen receptor T-cell therapy. *Pediatr Blood Cancer*. 2022;70:e29852.

How to cite this article: Huang S-M, Wan C-L, Cao H-Y, et al. Preemptive inotuzumab ozogamicin eradicated measurable residual disease in Ph-negative acute lymphoblastic leukemia relapsed post CD19 CART therapy. *Clin Case Rep*. 2023;11:e8289. doi:10.1002/ccr3.8289