Inotuzumab ozogamicin following allogeneic hematopoietic stem cell transplantation successfully rescued relapse of CD19 - negative acute lymphoblastic leukemia after CAR - T cell therapy

AUTHOR(S):

Kamitori, Tatsuya; Umeda, Katsutsugu; Akazawa, Ryo; Iwai, Atsushi; Obu, Satoshi; Isobe, Kiyotaka; Saida, Satoshi; ... Taga, Takashi; Adachi, Souichi; Takita, Junko

LETTER TO THE EDITOR

Inotuzumab ozogamicin following allogeneic hematopoietic stem cell transplantation successfully rescued relapse of CD19-negative acute lymphoblastic leukemia after CAR-T cell therapy

Tatsuya Kamitori[1], Katsutsugu Umeda[1*], Ryo Akazawa[1], Atsushi Iwai[1], Satoshi Obu[1], Kiyotaka Isobe[1], Satoshi Saida[1], Itaru Kato[1], Hidefumi Hiramatsu[1], Takashi Taga[2], Souichi Adachi[3], and Junko Takita[1]

[1]Department of Pediatrics[1], Graduate School of Medicine, Kyoto University, Kyoto, Japan
[2]Department of Pediatrics, Shiga University of Medical Science, Otsu, Japan
[3]Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan

*Correspondence to:
Katsutsugu Umeda, Department of Pediatrics, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan
Phone: +81-75-751-3290; Fax: +81-75-752-2361
Email address: umeume@kuhp.kyoto-u.ac.jp
Text word count: 748
Figures: 1

Short running head: InO and HSCT for relapse following CAR-T cell therapy

Keywords: Inotuzumab ozogamicin, hematopoietic stem cell transplantation, acute lymphoblastic leukemia, pediatric, chimeric antigen receptor T-cell therapy.

ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
BCP	B-cell precursor
BM	Bone marrow
BMT	Bone marrow transplantation
CAR	Chimeric antigen receptor
CR	Complete remission

GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
HSCT	Hematopoietic stem cell transplantation
InO	Inotuzumab ozogamicin
MRD	Minimal residual disease
RIC	Reduced-intensity conditioning
SOS	Sinusoidal obstruction syndrome
TAC	Tacrolimus
TBI	Total body irradiation

29

To the Editor: Anti-CD19 chimeric antigen receptor (CAR)-T cell therapy is one of the most promising treatment options for patients with relapsed/refractory B-cell precursor (BCP)-acute lymphoblastic leukemia (ALL).[1–3] Approximately 30–60% of patients experience relapse after CAR-T cell therapy, largely due to poor longevity of CAR-T cells and loss or downregulation of CD19 expression by leukemic cells.[4,5] The survival rate of these patients is extremely poor; however, there is no consensus regarding the best salvage treatment.[1]

Here, we report a 5-year-old boy with BCP-ALL harboring the *ETV6-RUNX1* rearrangement. He experienced a second bone marrow (BM) relapse 1 year after cord blood transplantation using a myeloablative conditioning regimen consisting of melphalan (180 mg/m^2) and fractionated total body irradiation (TBI; 12 Gy) in the second minimal residual disease (MRD)-negative complete remission (CR), defined as <0.01% by flow-cytometry. He was enrolled in the phase II, multicenter, global trial of CAR-T cell therapy (the ELIANA trial),[3] resulting in the third MRD-negative CR without complications (except for B-cell aplasia).

Unfortunately, he experienced a third BM relapse 1 year later at the age of 12. Since leukemic blasts were negative for CD19 but positive for CD22, he received Inotuzumab ozogamicin (InO) monotherapy. The off-label use of InO was approved by

the Patient Safety Unit, Kyoto University Hospital. The patient's family provided written informed consent before administration. Following one cycle of InO (0.8 mg/m^2 on day 1, and 0.5 mg/m^2 on days 8 and 15), he achieved a fourth MRD-negative CR. After a second cycle of InO (0.5 mg/m^2 on days 1, 8, and 15), he underwent T cell replete haploidentical BMT from his HLA-6/8 allele-matched father, using a reduced-intensity conditioning (RIC) regimen consisting of fludarabine (120 mg/m^2), cytarabine (6 g/m^2), and melphalan (180 mg/m^2). Tacrolimus (TAC), short-term methotrexate, prednisolone, and rabbit anti-thymocyte globulin (2.5 mg/kg) were used for graft-versus-host disease (GVHD).[6] Ursodeoxycolic acid, low molecular weight heparin, and antithrombin concentrate were administered for sinusoidal obstruction syndrome (SOS) prophylaxis.

Engraftment of neutrophils (>500/μL) and platelets (>50,000/μL) occurred on days 20 and 105, respectively, post-BMT. Complete chimerism in the BM was confirmed by the short tandem repeat method on day 28. On day 19, the patient developed a fever and hypoxia, and was diagnosed clinically as engraftment syndrome. Prednisolone was switched to methylprednisolone resulting in rapid improvement. Almost simultaneously, the patient became anemic and thrombocytopenic, leading to a clinical diagnosis of thrombotic microangiopathy based on elevation of lactate dehydrogenase (1,583 U/L), a decrease in haptoglobin (<2.0 mg/dL), and the presence of red blood cell fragmentation.

Rapid tapering of TAC and recombinant thrombomodulin administration led to an improvement. He also experienced severe BK virus-associated hemorrhagic cystitis on day 20, but improved over time after hematoma evacuation and bladder irrigation. No significant SOS or GVHD were observed. He remains in remission 2 years after BMT.

InO is a CD22-targeting humanized monoclonal antibody conjugated to the cytotoxic antibiotic calicheamicin.[7] In contrast to adult patients,[8] few reports have examined the efficacy and safety of InO in pediatric patients with relapsed/refractory BCP-ALL.[9–13] A retrospective analysis of 51 pediatric patients, all of whom received InO through the compassionate use program, demonstrated that 67% of patients achieved CR or CR with incomplete count recovery; the 12-month event-free survival and overall survival rates for the entire cohort were 23.4% and 36.3%, respectively.[9] The authors also demonstrated that the response to InO was independent of prior immunotherapy; however, they did not address clinical outcome and toxicity in patients that had received anti-CD19 CAR-T cell therapy. The patient reported herein harbored CD19-negative ALL cells that expressed high levels of CD22. As expected, InO exerted excellent anti-leukemia efficacy without severe complications and formed a bridge to subsequent allogeneic HSCT while the patient was in molecular CR. An alternative and promising option is anti-CD22 CAR-T cell therapy; however, this is not available in Japan.[14]

The patient received high-dose TBI prior to the first HSCT. The incidence of SOS is higher in pediatric patients than in adults undergoing HSCT after InO therapy, particularly patients who have received clofarabine and/or busulfan-containing conditioning regimens.[9] Therefore, we used a RIC regimen for subsequent HSCT. Of note, the patient remains in CR despite a lack of GVHD to achieve a substantial GVL effect. Thus, a large prospective study of larger populations is required to verify the clinical outcome (e.g., incidence and severity of GVHD and complications) of HSCT for patients who have received prior CAR-T cell therapy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

REFERENCES

1. 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.
2. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378:449-459.
3. Hiramatsu H, Adachi S, Umeda K, et al. Efficacy and safety of tisagenlecleucel in Japanese pediatric and young adult patients with relapsed/refractory B cell acute lymphoblastic leukemia. *Int J Hematol*. 2020;111:303-310.
4. Orlando EJ, Han X, Tribouley C, et al. Genetic mechanisms of target antigen loss in CAR19 therapy of acute lymphoblastic leukemia. *Nat Med*. 2018;24:1504-1506.
5. Xu X, Sun Q, Liang X, et al. Mechanisms of relapse after CD19 CAR T-cell therapy for acute lymphoblastic leukemia and its prevention and treatment strategies. *Front Immunol*. 2019;10:2664.
6. Mochizuki K, Kikuta A, Ito M, et al. Feasibility of tacrolimus, methotrexate, and prednisolone as a graft-versus-host disease prophylaxis in non-T-cell-depleted haploidentical hematopoietic stem cell transplantation for children. *Clin Transplant*. 2011;25:892-897.
7. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med*. 2016;25:740-753.
8. Jammal N, Chew S, Jabbour E, Kantarjian HM. Antibody based therapy in relapsed acute lymphoblastic leukemia. *Best Pract Res Clin Haematol*. 2020;33:101225.
9. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Leukemia*. 2019;33:884-892.
10. Fuster JL, Molinos-Quintana A, Fuentes C, et al. Blinatumomab and inotuzumab for B cell precursor acute lymphoblastic leukaemia in children: a retrospective study from the Leukemia Working Group of the Spanish Society of Pediatric Hematology and Oncology (SEHOP). *Br J Haematol*. 2020;190:764-771.
11. Calvo C, Cabanners-Hamy A, AdjaoudD, et al. Inotuzumab ozogamicin compassionate use for French paediatric patients with relapsed or refractory

CD22‐positive B‐cell acute lymphoblastic leukaemia. *Br J Haematol*. 2020;190:e53-e56.

12. Contreras CF, Higham CS, Behnert A, et al. Clinical utilization of blinatumomab and inotuzumab immunotherapy in children with relapsed or refractory B-acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2021;68:e28718.
13. Brivio E, Locatelli F, Lopez-Yurda M, et al. A Phase I study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study). *Blood*. [online ahead of print]
14. Fry TJ, Shah NN, Orentas RJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naïve or resistant to CD19-targeted CAR immunotherapy. *Nat Med*. 2018;24:20-28.

FIGURE LEGEND

FIGURE. Clinical course of haploidentical BMT.

Abbreviations: BMT, bone marrow transplantation; Flu, fludarabine; Ara-C, cytarabine; MEL, melphalan; ATG, anti-thymocyte globulin; LDH, lactate dehydrogenase; FRC, fragmented red blood cells; TAC, tacrolimus; PSL, prednisolone; mPSL, methylprednisolone; rTM, recombinant thrombomodulin.

Figure 1