LETTER TO THE EDITOR

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Daratumumab, Venetoclax, and Azacitidine in Combination with HAA Regimen as Consolidation Chemotherapy for T-cell Acute Lymphoblastic Leukemia with High CD38 Expression

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To the Editor

The combination of Venetoclax (Ven) and Azacitidine (Aza) may be effective for relapsed or refractory T-ALL (R/R T-ALL) [i,ii]. Researchers are exploring the use of Ven and/or Aza with AML-like chemotherapy regimens (e.g., HAG, CAG, FAI) for R/R T-ALL, including ETP and non-ETP subtypes [iii,iv,v]. The HAA regimen, composed of homoharringtonine (HHT), cytarabine (Ara-C), and Aclarubicin (Acla), has been commonly used in AML induction and salvage chemotherapy [vi,vii,viii]. We hypothesize that combining Ven and Aza with the HAA regimen (VA-HAA) may also exhibit therapeutic effects on T-ALL.

In addition, the therapeutic potential of the CD38 monoclonal antibody for T-ALL has gradually attracted attention [ix]. Biologically, CD38 expression is nearly ubiquitous in T-ALL cells. Up to 98% of T-ALL patients exhibit CD38-positive cells, and as many as 89% of patients display a CD38 positive expression rate exceeding 80%, which is significantly higher compared to B-ALL [x]. The frequent and stable expression of CD38 suggests that CD38-targeted therapy may offer significant potential in the treatment strategy for T-ALL [xi,xii,xiii]. Therefore, we exploratively employed a combination therapy consisting of Daratumumab (Dara) in conjunction with VA-HAA (Dara-VA-HAA) for a newly diagnosed (ND) T-ALL patient with high CD38 expression.

The patient was a 60-year-old female who was newly diagnosed with non-ETP-ALL in February 2024. This patient achieved complete remission (CR) after one cycle of VDLP induction chemotherapy but remained minimal residual disease (MRD) positive, with persistent high CD38 expression. Given the patient's insufficient depth of disease remission, there is a significant risk of relapse and a less favorable prognosis. After thorough discussion and comprehensive disclosure of the patient's condition by the physician, and following the acquisition of the patient's written informed consent, consolidation chemotherapy was initiated in April 2024 using the Dara-VA-HAA regimen (see *Supplementary Material*).

The patient experienced grade I/II adverse reactions, including headache, nausea, vomiting, and infusion-related reactions, all of which were fully resolved with appropriate symptomatic treatment. On day 11 of consolidation chemotherapy, chemotherapy-associated neutropenia, severe anemia, and thrombocytopenia were observed. To manage these complications, the patient received granulocyte colony-stimulating factor, recombinant human thrombopoietin, suspended red blood cell transfusions, and platelet apheresis transfusions for supportive care. By day 31, the ANC had recovered to greater than 1.0×10^9/L; by day 37, the PLT had recovered to greater than 100×10^9/L.

On day 32, BM MRD was negative, and the CD38 positivity rate had dropped to 0.00%. The disease status indicated CR with incomplete hematologic recovery (CRi). By day 73 of consolidation chemotherapy, both BM and cerebrospinal fluid (CSF) MRD were negative, with CD38 positivity rates of 0.00% in both samples. The disease status confirmed sustained CR. On day 78, the patient received preconditioning therapy with fludarabine and melphalan, followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT). The donor was the patient's son, who had a 7/12 HLA match, blood type O for B, negative donor-specific antibodies, and provided a CD34+ cell infusion dose of 13.35×10^6/kg. The chimerism rate was 94%.

As of November 2024, the patient has had undergone five consecutive BM MRD assessments that were all negative, with a CD38 positivity rate of 0.00%. NGS of the BM no longer detected the STAT5B mutation. CSF MRD remained negative. Both the neutrophil and platelet counts have recovered to within normal ranges. Treatment efficacy was assessed as CR. The patient was enrolled in another clinical trial for maintenance therapy following allo-HSCT, aimed at further reducing the risk of relapse. As of February 2025, the patient's disease status remained CR/MRD(-).

The combination of CD38 monoclonal antibody with chemotherapy may be one of the effective strategies for future T-ALL treatment [xiv]. It appears that combining Dara and Ven, which may have synergistic antitumor effects, with AML-like chemotherapy regimens could benefit T-ALL patients [xv]. However, HHT can exert anti-leukemic activity against T-ALL by inhibiting the NOTCH/MYC pathway, thereby extending the survival of T-ALL xenograft models, suggesting that HHT is also a potential therapeutic agent for T-ALL [xvi]. Moreover, HHT may enhance the efficacy of Ven and Aza by improving chemotherapy sensitivity [xvii, xviii]. Therefore, we believe that the Dara-VA-HAA may be effective and safe for treating T-ALL.

Based on the aforementioned hypothesis, we conducted an exploratory Dara-VA-HAA consolidation therapy for a T-ALL patient who was evaluated as CR/MRD(+) with high CD38 expression following induction chemotherapy. This manuscript may present the first global case report on using Dara-VA-HAA for ND T-ALL. It could be a viable pre-allo-HSCT consolidation option for T-ALL patients. Given the limited evidence from case reports, we remain cautiously optimistic and advocate for further clinical studies with larger cohorts to validate its efficacy and safety.

Ethics and informed consent

The clinical pathway strictly adhered to the Declaration of Helsinki, relevant clinical practice guidelines, and the laws and regulations of the People's Republic of China. It was approved by the Ethics Committee of the 920th Hospital of the Joint Logistics Support Force (No. 2022-096-02). Before consolidation therapy and prior to drafting this manuscript, the patient provided written informed consent. The retrospective analysis was approved by the Ethics Committee of the Sixth Affiliated Hospital of Kunming Medical University (No. 2024kmykdx6f201).

Competing interests

The authors declare that they have no competing interests.

Data Availability Statement

All data obtained and analyzed in this study are available from the corresponding authors upon reasonable request. Patient personal information is not publicly available due to privacy and ethical restrictions.

Authorship contribution statement

L.F. and S.W.: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing-original draft, Writing-review & editing. **H.L.:** Supervision, Validation. **A.T.:** Writing-original draft, Writing-review & editing. **M.X.:** Data curation.

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References

[i] Wan CL, Zou JY, Qiao M, et al. Venetoclax combined with azacitidine as an effective and safe salvage regimen for relapsed or refractory T-cell acute lymphoblastic leukemia: a case series. *Leuk Lymphoma*. 2021; 62(13): 3300-3303. doi:10.1080/10428194.2021.1957876

[ii] Jeanselme P, Tavitian S, Lapierre L, et al. Long-term exposure and response to azacitidine for post-hematopoietic stem cell transplantation relapse of early T-cell precursor acute lymphoblastic leukemia: a case report and review

of the literature. *Leuk Lymphoma*. 2024; 65(13): 2025-2030. doi: 10.1080/10428194.2024.2390572

[iii] Zhang X, Li J, Jin J, Yu W. Relapsed/refractory early T-cell precursor acute lymphoblastic leukemia was salvaged by venetoclax plus HAG regimen. *Ann Hematol*. 2020;99(2):395-397. doi:10.1007/s00277-019-03902-9

[iv] Zhao Y, Jiang S, Tang Y, Zhao L. Venetoclax with CAG regimen for early T-cell precursor acute lymphoblastic leukemia: a case report and literature review. *Int J Hematol*. 2023; 118(4): 483-488. doi: 10.1007/s12185-023-03623-w

[v] Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical Experience With Venetoclax Combined With Chemotherapy for Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia. *Clin Lymphoma Myeloma Leuk*. 2020; 20(4): 212-218. doi:10.1016/j.clml.2019.09.608

[vi] Jin J, Wang JX, Chen FF, et al. Homoharringtonine-based induction regimens for patients with de-novo acute myeloid leukaemia: a multicentre, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2013; 14(7): 599-608. doi: 10.1016/S1470-2045(13)70152-9

[vii] Yu W, Mao L, Qian J, et al. Homoharringtonine in combination with cytarabine and aclarubicin in the treatment of refractory/relapsed acute myeloid leukemia: a single-center experience. *Ann Hematol*. 2013; 92(8): 1091-1100. doi: 10.1007/s00277-013-1758-5

[viii] Duan W, Yang S, Zhao T, et al. Comparison of efficacy between homoharringtonine, aclarubicin, cytarabine (HAA) and idarubicin, cytarabine (IA) regimens as induction therapy in patients with de novo core binding factor acute myeloid leukemia. *Ann Hematol*. 2023; 102(10): 2695-2705. doi: 10.1007/s00277-023-05400-5

[ix] Bride KL, Vincent TL, Im SY, et al. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. *Blood*. 2018;131(9): 995-999. doi:10.1182/blood-2017-07-794214

[x] Fang J, Zhang R, Lin X, Xu Y, Huang K, Saw PE. Aberrant expression of T cell activation markers and upregulation of Tregs in bone marrow and peripheral blood in acute myeloid leukemia patients. *Hematology*. 2023; 28(1): 2219554. doi: 10.1080/16078454.2023.2219554

[xi] Liao C, Wang Y, Huang Y, et al. CD38-Specific CAR Integrated into CD38 Locus Driven by Different Promoters Causes Distinct Antitumor Activities of T and NK Cells. *Adv Sci (Weinh)*. 2023; 10(27): e2207394. doi:10.1002/advs.202207394

[xii] Glisovic-Aplenc T, Diorio C, Chukinas JA, et al. CD38 as a pan-hematologic target for chimeric antigen receptor T cells. *Blood Adv*. 2023; 7(16): 4418-4430. doi:10.1182/bloodadvances.2022007059

[xiii] Prejzner W, Piekoś O, Bełdzińska K, et al. The role of daratumumab in relapsed/refractory CD38 positive acute leukemias-case report on three cases with a literature review. *Front Oncol*. 2023; 13: 1228481. doi:10.3389/fonc.2023.1228481

[xiv] Dai Y, Luo L, Wei Z, Cheng P, Luo J, Li J. The clinical efficacy of a daratumumab-based regimen in relapsed/refractory acute leukemia: a single-center experience. *Ann Hematol*. 2024; 103(10): 4057-4063. doi:10.1007/s00277-024-05892-9

[xv] Shi H, Yang F, Cao M, et al. Daratumumab and venetoclax combined with CAGE for late R/R T-ALL/LBL patients: Single-arm, open-label, phase I study. *Ann Hematol*. 2024; 103(8): 2993-3004. doi:10.1007/s00277-024-05775-z

[xvi] Suo S, Zhao D, Li F, et al. Homoharringtonine inhibits the NOTCH/MYC pathway and exhibits antitumor effects in T-cell acute lymphoblastic leukemia. *Blood*. 2024; 144(12): 1343-1347. doi: 10.1182/blood.2023023400

[xvii] Yin Z, Yao Z, Chen D, et al. Homoharringtonine may help improve the outcomes of venetoclax and azacitidine in AML1-ETO positive acute myeloid leukemia. *J Cancer Res Clin Oncol*. 2024; 150(7): 336. doi: 10.1007/s00432-024-05861-9

[xviii] Jin H, Zhang Y, Yu S, et al. Venetoclax Combined with Azacitidine and Homoharringtonine in Relapsed/Refractory AML: A Multicenter, Phase 2 Trial. *J Hematol Oncol*. 2023; 16(1): 42. doi: 10.1186/s13045-023-01437-1