

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

Yüksek CD38 ifadeli T-hücreli Akut Lenfoblastik Lösemide Pekistirme Kemoterapisi Olarak HAA Rejimiyle Kombine Daratumumab, Venetoklaks ve Azasitidin

Lin-Sen Feng^{1,2,3,4}, Hui-Yuan Li⁵, Ai Tang⁴, Meng-Li Xu², San-Bin Wang²

¹The Sixth Affiliated Hospital, Kunming Medical University, Department of Hematology, Yunnan, P.R. China

²The 920th Hospital of Joint Logistics Support Force, Department of Hematology, Yunnan, P.R. China

³The People's Hospital of Yuxi City, Department of Hematology, Yunnan, P.R. China

⁴Kunming Medical University, School of General Practitioners, Department of Hematology, Yunnan, P.R. China

⁵The First People's Hospital of Yunnan Province, Department of Integrated Traditional Chinese Medicine and Western Medicine, Yunnan, P.R. China

To the Editor,

The combination of venetoclax (Ven) and azacitidine (Aza) may be effective for relapsed or refractory (R/R) T-cell acute lymphoblastic leukemia (T-ALL) [1,2]. Researchers are exploring the use of Ven and/or Aza with acute myeloid leukemia (AML)-like chemotherapy regimens such as HAG (comprising homoharringtonine, cytarabine, and granulocyte colony-stimulating factor), CAG (comprising cytarabine, aclarubicin, and granulocyte colony-stimulating factor), and FAI (comprising fludarabine, cytarabine, and idarubicin) for R/R T-ALL, including cases of both early T-cell precursor (ETP) and non-ETP subtypes [3,4,5]. The HAA regimen, comprising homoharringtonine, cytarabine, and aclarubicin, has been commonly used in AML induction and salvage chemotherapy [6,7,8]. We hypothesized that combining Ven and Aza with the HAA regimen (VA-HAA) could also achieve therapeutic effects in cases of T-ALL.

In addition, the therapeutic potential of the CD38 monoclonal antibody for the treatment of T-ALL has been gradually attracting increased attention [9]. Biologically, CD38 expression is nearly ubiquitous in T-ALL cells. Up to 98% of T-ALL patients have CD38-positive cells, and as many as 89% of patients display a CD38 positivity expression rate exceeding 80%, which is significantly higher compared to B-cell ALL [10]. The frequent and stable expression of CD38 in T-ALL suggests that CD38-targeted therapy may offer significant treatment potential [11,12,13]. Therefore, we exploratively employed a combination therapy consisting of daratumumab (Dara) in conjunction with VA-HAA (Dara-VA-HAA) for a newly diagnosed T-ALL patient with high CD38 expression.

The patient was a 60-year-old woman who was newly diagnosed with non-ETP ALL in February 2024. She achieved complete remission (CR) after one cycle of vincristine, daunorubicin, L-asparaginase, and prednisone induction chemotherapy but remained positive for minimal residual disease (MRD) with persistent high CD38 expression. Given the patient's insufficient depth of disease remission, there was a significant risk of relapse and a less favorable prognosis. After thorough discussion and comprehensive disclosure of the patient's condition by her 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.

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, her absolute neutrophil count had recovered to greater than $1.0 \times 10^9/L$, and by day 37, her platelet count had recovered to greater than $100 \times 10^9/L$.

On day 32, the bone marrow was negative for MRD and the CD38 positivity rate had dropped to 0.00%. The disease status indicated CR with incomplete hematologic recovery. By day

73 of consolidation chemotherapy, both the bone marrow and cerebrospinal fluid were negative for MRD, with CD38 positivity rates of 0.00% for both samples. The disease status indicated 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 human leukocyte antigen match, blood type O for B, and negative donor-specific antibodies. He provided a CD34-positive cell infusion dose of $13.35 \times 10^6/\text{kg}$. The chimerism rate was 94%.

As of November 2024, the patient had undergone five consecutive bone marrow assessments for MRD, all of which were negative, with a CD38 positivity rate of 0.00%. Next-generation sequencing of the bone marrow no longer detected the *STAT5B* mutation. The cerebrospinal fluid also remained negative for MRD. Both the neutrophil and platelet counts had recovered to within the 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 with MRD negativity.

The combination of CD38 monoclonal antibody with chemotherapy may be an effective strategy for future T-ALL treatment [14]. It appears that combining Dara and Ven, which may have synergistic antitumor effects, with AML-like chemotherapy regimens could benefit T-ALL patients [15]. Homoharringtonine can also exert anti-leukemic activity against T-ALL by inhibiting the NOTCH/MYC pathway, thereby extending the survival of T-ALL xenograft models, suggesting that homoharringtonine is also a potential therapeutic agent for T-ALL [16]. Moreover, homoharringtonine may enhance the efficacy of Ven and Aza by improving chemotherapy sensitivity [17,18]. Therefore, we believe that the Dara-VA-HAA regimen may be effective and safe for treating T-ALL.

Based on our hypothesis, we administered exploratory Dara-VA-HAA consolidation therapy for a T-ALL patient whose status was evaluated as CR/MRD+ with high CD38 expression following induction chemotherapy. This letter may constitute the world's first case report on the use of Dara-VA-HAA for newly diagnosed T-ALL. Dara-VA-HAA could be a viable pre-allo-HSCT consolidation option for T-ALL patients. Given the limited relevant evidence from case reports, we remain cautiously optimistic and advocate further clinical studies with larger cohorts to validate this regimen's efficacy and safety.

Keywords: T-cell acute lymphoblastic leukemia, Consolidation, Daratumumab, Venetoclax, Azacitidine

Anahtar Sözcükler: T-hücreli akut lenfoblastik lösemi, Pekıştirme, Daratumumab, Venetoklaks, Azasitidin

Ethics

Informed Consent: Before receiving consolidation therapy and prior to the drafting of this manuscript, the patient provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: L-S.F., H-Y.L., S-B.W.; Concept: L-S.F., S-B.W.; Design: S-B.W.; Data Collection or Processing: L-S.F., H-Y.L., A.T., M-L-X., S-B.W.; Analysis or Interpretation: L-S.F., S-B.W.; Literature Search: L-S.F., H-Y.L., A.T., S-B.W.; Writing: L-S.F., A.T., S-B.W.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by grants from the Yunnan Applied Basic Research Projects-Union Foundation (no.: 202201AY070001-278) and the Yunnan Province High-Level Talents Training Support Plan "Famous Doctors Special Project."

References

- Wan CL, Zou JY, Qiao M, Yin J, Shen XD, Qiu QC, Liu SB, Xue SL. 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;62:3300-3303.
- Jeanselmie P, Tavitian S, Lapierre L, Vergez F, Rigolot L, Huynh A, Bertoli S, Delabesse E, Huguet F. 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;65:2025-2030.
- 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;99:395-397.
- 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;118:483-488.
- Richard-Carpentier G, Jabbour E, Short NJ, Rausch CR, Savoy JM, Bose P, Yilmaz M, Jain N, Borthakur G, Ohanian M, Alvarado Y, Rytting M, Kebriaei P, Konopleva M, Kantarjian H, Ravandi F. Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk*. 2020;20:212-218.
- Jin J, Wang JX, Chen FF, Wu DP, Hu J, Zhou JF, Hu JD, Wang JM, Li JY, Huang XJ, Ma J, Ji CY, Xu XP, Yu K, Ren HY, Zhou YH, Tong Y, Lou YJ, Ni WM, Tong HY, Wang HF, Mi YC, Du X, Chen BA, Shen Y, Chen Z, Chen SJ. Homoharringtonine-based induction regimens for patients with de-novo acute myeloid leukaemia: a multicentre, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2013;14:599-608.
- Yu W, Mao L, Qian J, Qian W, Meng H, Mai W, Tong H, Tong Y, Jin J. Homoharringtonine in combination with cytarabine and aclarubicin in the treatment of refractory/relapsed acute myeloid leukemia: a single-center experience. *Ann Hematol*. 2013;92:1091-1100.
- Duan W, Yang S, Zhao T, Hu L, Qin Y, Jia J, Wang J, Lu S, Jiang H, Zhang X, Xu L, Wang Y, Lai Y, Shi H, Huang X, Jiang Q. 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;102:2695-2705.
9. Bride KL, Vincent TL, Im SY, Aplenc R, Barrett DM, Carroll WL, Carson R, Dai Y, Devidas M, Dunsmore KP, Fuller T, Glisovic-Aplenc T, Horton TM, Hunger SP, Loh ML, Maude SL, Raetz EA, Winter SS, Grupp SA, Hermiston ML, Wood BL, Teachey DT. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. *Blood.* 2018;131:995-999.
 10. Koslowski S, Glauben R, Habringer S, Burmeister T, Keller U, Brüggemann M, Gökbüget N, Schwartz S. Frequent, high density expression of surface CD38 as a potential therapeutic target in adult T-lineage acute lymphoblastic leukemia. *Haematologica.* 2024;109:661-665.
 11. Liao C, Wang Y, Huang Y, Duan Y, Liang Y, Chen J, Jiang J, Shang K, Zhou C, Gu Y, Liu N, Zeng X, Gao X, Tang Y, Sun J. 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:e2207394.
 12. Glisovic-Aplenc T, Diorio C, Chukinas JA, Veliz K, Shestova O, Shen F, Nunez-Cruz S, Vincent TL, Miao F, Milone MC, June CH, Teachey DT, Tasian SK, Aplenc R, Gill S. CD38 as a pan-hematologic target for chimeric antigen receptor T cells. *Blood Adv.* 2023;7:4418-4430.
 13. Prejzner W, Piekos O, Beldzińska K, Sadowska-Klasa A, Zarzycka E, Bieniaszewska M, Lewandowski K, Zaucha JM. 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.
 14. 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;103:4057-4063.
 15. Shi H, Yang F, Cao M, Xu T, Zheng P, Guo Y, Su G, Feng S, Li R, Liu R, Liu H, Ma L, Ke X, Hu K. Daratumumab and venetoclax combined with CAGE for late R/R T-ALL/LBL patients: single-arm, open-label, phase I study. *Ann Hematol.* 2024;103:2993-3004.
 16. Suo S, Zhao D, Li F, Zhang Y, Rodriguez-Rodriguez S, Nguyen LXT, Ghoda L, Carlesso N, Marcucci G, Zhang B, Jin J. Homoharringtonine inhibits the NOTCH/MYC pathway and exhibits antitumor effects in T-cell acute lymphoblastic leukemia. *Blood.* 2024;144:1343-1347.
 17. Yin Z, Yao Z, Chen D, Zhang Y, Weng G, Du X, Lin D, Xiao J, Sun Z, Zhang H, Liang X, Guo Z, Zhao W, Xuan L, Jiang X, Shi P, Liu Q, Ping B, Yu G. Homoharringtonine may help improve the outcomes of venetoclax and azacitidine in AML1-ETO positive acute myeloid leukemia. *J Cancer Res Clin Oncol.* 2024;150:336.
 18. Jin H, Zhang Y, Yu S, Du X, Xu N, Shao R, Lin D, Chen Y, Xiao J, Sun Z, Deng L, Liang X, Zhang H, Guo Z, Dai M, Shi P, Huang F, Fan Z, Yin Z, Xuan L, Lin R, Jiang X, Yu G, Liu Q. Venetoclax combined with azacitidine and homoharringtonine in relapsed/refractory AML: a multicenter, phase 2 trial. *J Hematol Oncol.* 2023;16:42.



Address for Correspondence/Yazışma Adresi: San-Bin Wang, M.D., The 920th Hospital of Joint Logistics Support Force, Department of Hematology, Yunnan, P.R. China
E-mail: sanbin1011@163.com ORCID: orcid.org/0000-0002-4802-0292

Received/Geliş tarihi: January 14, 2025

Accepted/Kabul tarihi: May 5, 2025

DOI: 10.4274/tjh.galenos.2025.2025.0019



©Copyright 2025 by Turkish Society of Hematology Turkish Journal of Hematology, Published by Galenos Publishing House.
Licensed under a Creative Commons Attribution-NonCommercial (CC BY-NC-ND) 4.0 International License.