LETTER TO THE EDITOR

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Anti-CD22 Calicheamicin-Inotuzumab Ozogamicin Combined with Venetoclax + Azacitidine in the Treatment of Mixed-Phenotype Acute Leukemia: A Case Report

Mikst Fenotip Akut Lösemi Tedavisinde Kalikamisin-Inotuzumab Ozogamisin ile Kombine Venetoclax + Azasitidin Rejimi: Olgu Sunumu

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To the Editor,

Mixed-phenotype acute leukemia (MPAL) is an unusual subtype of leukemia that can involve more than one lineage-defining marker in a single blast population (biphenotypic) or two or more identifiable single-lineage leukemia populations (bilineal) [1,2]. The prognosis of MPAL is poor and its optimum treatment is still debated. Here we report a challenging case of mixed-lineage acute leukemia (MLAL)/MPAL in a patient with two blast populations, entailing both biphenotypic and bilineal characteristics, successfully treated with anti-CD22 calicheamicin conjugate-inotuzumab ozogamicin (InO) and venetoclax plus azacitidine (VA). The authors confirm that the patient consented to have his case presented in a publication. To protect the patient's privacy, all information is presented anonymously.

A 57-year-old patient was diagnosed with MLAL after presenting with hyperleukocytosis and anemia. Bone marrow morphology testing showed 86% lymphoid blasts. Flow cytometry analysis revealed that 70% of the cell population exhibited the immunophenotype of $CD13^+$, $CD117^+$, $CD7^+$, $CD34^+$, $CD22^+$, $CD19p^+$, $CD79ap^+$, and $CD45^{dim}$, while another 15% of the population displayed the immunophenotype of $CD7^+$, $CD13^+$, $CD34^+$, $CD117^+$, $HLA\text{-}DR^+$, and $CD33p^+$. The chromosome abnormality of 43-46,Y,t(X;1)(q28; q24) and genetic abnormality of *NRAS* p.G13D (variant allele frequency: 26%) and p.G12D (variant allele frequency: 10.8%) were observed. VDPCP (vinblastine at 2 mg on days 1, 8, and 15; idarubicin at 13 mg on days 1-3; pegaspargase at 3750 IU on day 8; cyclophosphamide at 1200 mg on day 1; methylprednisolone at 60 mg on days 1-14) was used as induction chemotherapy for the patient. On day 14 of chemotherapy, bone marrow testing showed myelosuppression with 27% blasts, indicating that the patient had failed to achieve remission. The patient then received low-dose cytarabine (25 mg every 12 h on days 17-23), which was halted due to 4th degree bone marrow depression and stomachache. He was then transferred to our department for further treatment. On day 33 following the initial chemotherapy, the bone marrow showed 28% residual blasts and flow cytometry revealed a population of 20.7% of cells with the following immunophenotype: $CD45^{dim}$, $CD13^+$, $CD117^+$, $CD7^+$, $CD34^+$, $HLA\text{-}DR^+$, $nTDT^+$,$CD22str^+$, $CD33p^+$, $CD13p^+$, $CD19p^+$, and $cCD79^+$ (60.2%). While 60.2% did not express CD20, CD10, CyCD3, CD64, CD14, CD4, or MPO, another 5.95% of the population had the following immunophenotype: $CD13^+$, $CD34^+$, $CD117^+$, $HLA\text{-}DR^+$, $CD33p^+$, and $MPOp^+$ (Figure 1). Based on the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours [3], this patient with $CD19^+$ and $CD22^+CD79a^+$ (>50%) characteristics with myeloid expression was diagnosed with MPAL, B/myeloid. A new treatment strategy with InO and VA was administered. InO was administered at 0.65 mg/m^2 once weekly for 2 weeks, azacitidine was administered at 75 mg/m^2 once daily for 7 days, and venetoclax was administered for 14 days. On day 14 after the beginning of the new treatment strategy, routine bone marrow testing revealed myelosuppression without blasts and flow cytometry revealed a 0.015% population of primitive B/myeloid dual-phenotype cells. The patient was then rapidly scheduled to undergo a half-related allogeneic hematopoietic stem cell transplantation. He continued to maintain molecular remission for 8 months following transplantation.

InO was found to be effective and well tolerated in patients with relapsed or refractory acute lymphoblastic leukemia (ALL)

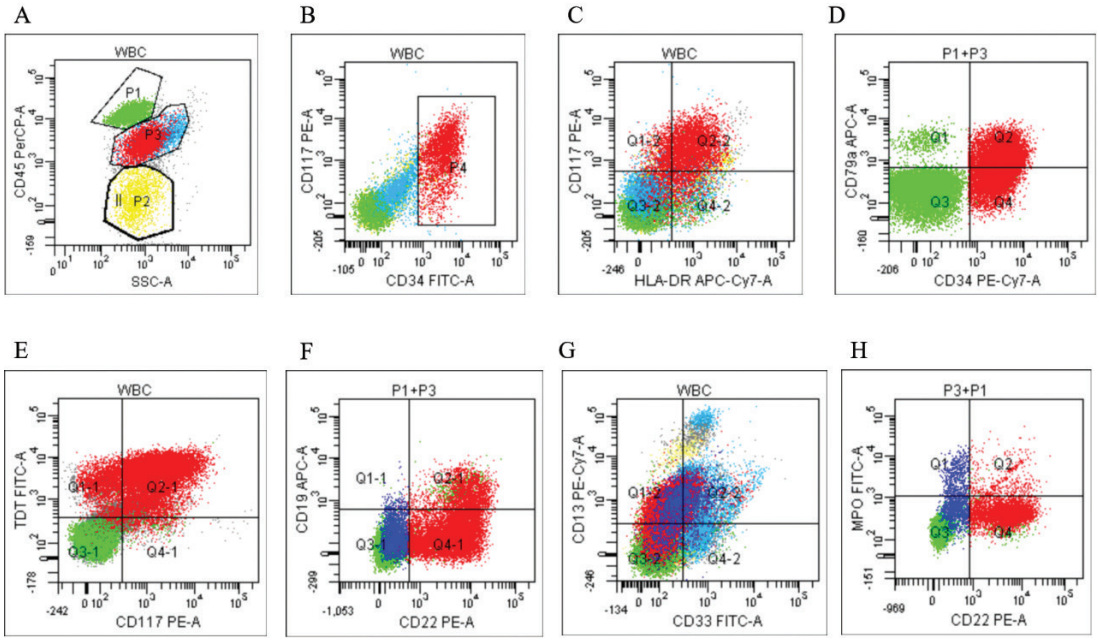

Figure 1. Mixed-phenotype acute leukemia, B/myeloid, with biphenotypic blasts. (A) Abnormal primitive cells (red cell population) accounted for 20.7% of the nucleated cells; abnormal primitive myeloid cells (navy blue cell population) accounted for 5.95% of the nucleated cells. (B-H) Abnormal primitive cells: expression of CD34, CD117, CD22str, CD13, HLA-DR, nTDT, and CD7 with partial expression of CD19, CD33, CD38, and cCD79a, considered to reflect primitive B/myeloid dual-phenotype cells; abnormal primitive myeloid: expression of CD34, CD117, CD13, nTDT, CD7, and HLA-DR with partial expression of CD33, MPO and CD38 and no expression of CD19, CD10, CD22, or CyCD3.

FITC: Fluorescein isothiocyanate; Cy7: cyanine 7; PE: phycoerythrin; SSC: side scatter; TdT: terminal deoxynucleotidyl transferase; APC: allophycocyanin; WBC: white blood cells.

[4]. Venetoclax has been increasingly used in the treatment of leukemia, with more applications in ALL [4], and it is a potent and highly selective B-cell lymphoma-2 (BCL-2) inhibitor. It induces apoptosis in leukemia cells by inhibiting BCL-2 and it is often used in combination with other drugs such as azacitidine [6]. Some studies have demonstrated that venetoclax in combination with InO in B-lineage ALL has a synergistic effect [7]. VA as an emerging therapy has shown promising efficacy in AML [8,9]. The innovative combination of InO and VA appears to be a promising therapeutic approach for MPAL, even in refractory cases. However, in this report, it was applied for only one patient, and a larger sample of studies is still needed to determine the effectiveness of this combination.

Keywords: Mixed-phenotype acute leukemia, Targeted therapy, Inotuzumab ozogamicin

Anahtar Sözcükler: Mikst fenotip akut lösemi, Hedefe yönelik tedavi, İnotuzumab ozogamisin

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Authorship Contributions

Surgical and Medical Practices: K.L.; Concept: Y.L.; Design: Y.W.; Data Collection or Processing: R.P., J.C.; Analysis or Interpretation: B.Z., J.L.; Literature Search: K.L., X.Z.; Writing: Y.W.

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

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