

Long-Term Complete Remission Following Lenalidomide-Augmented IVAC/ICE Therapy and Allogeneic Hematopoietic Stem Cell Transplantation in Hepatosplenic T-Cell Lymphoma: A Case Report

Hepatosplenik T-Hücreli Lenfomada Lenalidomid ile Güçlendirilmiş IVAC/ICE Tedavisi ve Allojenik Hematopoietik Kök Hücre Nakli Sonrası Uzun Süreli Tam Remisyon: Bir Olgu Sunumu

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Dear Editor,

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive subtype of peripheral T-cell lymphoma (PTCL) that typically affects young males and is characterized by hepatosplenomegaly, cytopenias and poor outcomes. We report a case of HSTCL achieving complete remission (CR) following lenalidomide-augmented IVAC/ICE (IVAC: ifosfamide, etoposide, high-dose cytarabine; ICE: ifosfamide, carboplatin, etoposide) and consolidation with allogeneic hematopoietic stem cell transplantation (allo-HSCT).

A 21-year-old male patient presented in September 2022 with complaints of fatigue, weakness and fever. Laboratory evaluations revealed pancytopenia and ultrasound showed hepatosplenomegaly (spleen 17 cm, liver 19 cm). A bone marrow aspiration biopsy was performed for diagnosis and revealed HSTCL ($\gamma\delta$ T-cell phenotype). Positron emission tomography/computed tomography (PET-CT) performed for staging showed no fluorodeoxyglucose (FDG)-uptake lesions in any region, only diffuse non-homogeneous bone marrow involvement. Cytogenetic analysis revealed no structural or numerical abnormalities; however, fluorescence in situ hybridization detected trisomy 8q24 in 30% of cells and next-generation sequencing identified a KRAS mutation with a variant allele frequency of 20.7%. Cerebrospinal fluid cytology and flow cytometry were negative for central nervous system involvement.

In October 2022, treatment was initiated with an alternating IVAC and ICE regimen (IVAC/ICE), consisting of two cycles of IVAC and two cycles of ICE, for a total of four cycles, with the addition of lenalidomide at a dose of 25 mg/day for 14 days per cycle (lenalidomide-augmented IVAC/ICE) to enhance cytotoxic and immunomodulatory activity. Prophylactic pegfilgrastim, trimethoprim–sulfamethoxazole, and valaciclovir were administered. Low-molecular-weight heparin thromboprophylaxis was continued until the platelet count decreased below $50 \times 10^9/L$. The patient experienced one episode of neutropenic fever after the first lenalidomide-augmented IVAC cycle, which was successfully treated with meropenem and teicoplanin. After completion of four cycles of lenalidomide-augmented IVAC/ICE, PET-CT and bone marrow biopsy demonstrated complete metabolic and morphological remission.

On 2 February 2023, following a conditioning regimen comprising cyclophosphamide (60 mg/kg/day on days –5 and –4) and total-body irradiation (total 12 Gy; 2×2 Gy/day on days –3 to –1), an allo-HSCT was performed using an 8-year-old male sibling donor who was human leukocyte antigen (HLA)-matched. A total of 4.3×10^6 CD34⁺ cells/kg of peripheral blood stem cells were infused. Methotrexate and cyclosporine were administered for graft-versus-host disease prophylaxis. Neutropenic fever and grade 2 mucositis developed on day +6 post-transplantation. Neutrophil engraftment was achieved on day +13. Intravenous ganciclovir at a dose of 5 mg/kg twice daily was initiated on day +15 due to cytomegalovirus reactivation. Complete donor chimerism was observed on day +30 and

platelet engraftment occurred on day +33. Post-transplant bone marrow biopsy and PET-CT demonstrated CR. The patient has maintained full donor chimerism and remains in CR at 34 months post-transplantation, without evidence of graft-versus-host disease or relapse. No lenalidomide maintenance therapy was administered.

Discussion

A meta-analysis conducted by Klebaner et al. demonstrated that non-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) induction regimens provided a significant advantage in terms of both response rate and survival outcomes [1]. Consequently, there is a growing approach to the use of intensive regimens containing cytarabine, etoposide and platinum. The use of intensive induction regimens is critical for achieving deep response for allo-HSCT. Indeed, allo-HSCT is recommended after initial remission in all patients where possible [2]. Lenalidomide exerts anti-lymphoma activity not only through direct cytotoxic mechanisms but also by modulating the tumor immune microenvironment. It enhances T-cell and natural killer cell function, regulates cytokine signaling, and improves immune synapse formation, thereby promoting antitumor immune responses. In T-cell lymphomas, these immunomodulatory effects provide a biological rationale for combination strategies, where lenalidomide may enhance both the depth and durability of responses achieved with cytotoxic therapy. Although certain molecular findings such as trisomy 8q24 and KRAS mutation may reflect aggressive disease biology, they are not validated biomarkers to guide the use of lenalidomide. The rationale for adding lenalidomide in our case was not to further intensify cytotoxicity, but to enhance immune-mediated anti-lymphoma effects. In addition, its demonstrated clinical activity in R/R PTCL and its evaluation in combination regimens such as CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) support its potential role as a combinatorial agent, although evidence in HSTCL remains limited [3–5].

In this context, it is noteworthy that in our case, lenalidomide-augmented IVAC/ICE induction therapy achieved complete morphological and metabolic remission after two cycles. Together with our previously reported case demonstrating durable disease control with single-agent lenalidomide, the present observation further supports a potential role for lenalidomide across different treatment settings in HSTCL [6]. However, there is no report in the literature describing remission in HSCTL following the lenalidomide-augmented IVAC/ICE; therefore, this case presents a unique clinical observation suggesting synergy between lenalidomide augmentation and intensive cytotoxic therapy. Following the achievement of CR, our patient was consolidated with allo-HSCT from a HLA-matched sibling donor at the optimal time. The patient remains in CR at 34 months of follow-up. This outcome is consistent with published data in HSTCL demonstrating that achievement of an early and deep remission enabling timely hematopoietic stem cell transplantation is a key determinant of durable disease control and long-term survival [1,7,8].

In conclusion, this case demonstrates that lenalidomide augmentation of intensive cytarabine–platinum–etoposide–based therapy, such as IVAC/ICE, in HSTCL can provide a rapid response and enable successful bridging to transplantation. This finding points to an innovative treatment approach that warrants evaluation in prospective studies.

Keywords: Hepatosplenic T-cell lymphoma; Lenalidomide; IVAC/ICE; Allogeneic Hematopoietic stem cell transplantation; Peripheral T-cell lymphoma

Anahtar Kelimeler: Hepatosplenik T-hücreli lenfoma, Lenalidomid, IVAC/ICE, Allojenik kök hücre nakli

Footnotes:

Informed consent

Informed consent for publication was obtained from the patient. All the authors have reviewed the manuscript and approved it for publication.

Authorship Contributions

Surgical and Medical Practices: S.Y.K., L.K., H.S.B.; Concept: S.Y.K.; Design: R.A., S.Y.K.; Data Collection or Processing: S.Y.K., A.Ç., H.S.B.; Analysis or Interpretation: S.Y.K., L.K.; Literature Search: R.A., S.Y.K.; Writing: R.A., S.Y.K., L.K.

Conflict of interest

The authors declare that they have no conflict of interest.

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