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Case Report

Successful Bridging to Allogeneic Transplantation With Valemetostat in Two Refractory/relapsed Peripheral T-cell lymphoma patients

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Abstract. We report the case of 2 patients with relapsed/refractory peripheral T-cell lymphoma treated with valemetostat tosylate, a selective dual inhibitor of histone-lysine N-methyltransferases enhancer of zest homolog 1 and 2, and subsequently bridged to allogeneic stem cell transplantation. Valemetostat led to a quick response and was well tolerated, offering a promising bridge therapy to transplantation for patients with relapsed/refractory peripheral T-cell lymphoma, which is still an unmet medical need.

Keywords: Valemetostat; Peripheral T-cell Lymphoma; Allogeneic Transplantation; Refractory Disease.

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Introduction. Relapsed/refractory peripheral T-cell lymphoma (R/R PTCL) has a poor prognosis, with a median overall survival (OS) of approximately 6 months.[1-3] The achievement of a meaningful response and subsequent allogeneic stem cell transplantation (allo-SCT) remains the only approach that can overcome the dismal prognosis of the disease, reaching a 5-year OS and progression-free survival (PFS) of approximately 50% and 40%, respectively.[4]

New emerging drugs, which may lead to a complete response (CR), have a key role as a bridge therapy to allo-SCT, given that the presence of active disease before allo-SCT significantly correlates with a higher relapse rate.[5]

We report the case of 2 patients with R/R PTCL treated with valemetostat tosylate, a selective dual inhibitor of histone-lysine N-methyltransferases enhancer of zest homolog 1 and 2 (EZH1/2) as a bridge therapy to allo-SCT. Patients gave consent to publish their data.

Case Presentation

Case #1. A 63-year-old Caucasian man was diagnosed with PTCL with T follicular helper (TFH) phenotype, not otherwise specified, EBV negative, stage IIIA in November 2019. He was treated with CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) for 6 cycles from December to April 2019, achieving a partial response. Then he received brentuximab vedotin for 9 cycles from June to December 2019, obtaining a stable disease. Therefore, the patient was treated with 8 cycles of gemcitabine plus cisplatin from June to December 2020, resulting in disease progression (PD).

The patient was then referred to our center, where he received ASTX-660, a novel non-peptidomimetic

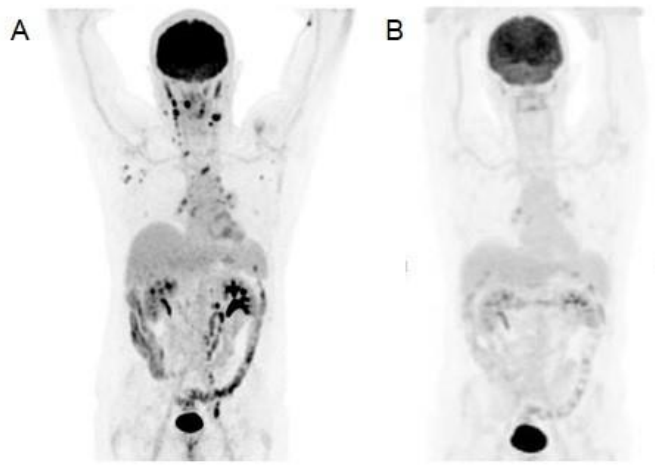

Figure 1. Case 1. Positron Emission Tomography imaging before (**A**) and after (**B**) valemetostat.

antagonist of apoptosis proteins (cIAP1/2 and XIAP), 90 mg BID for 2 cycles from April to June 2021, resulting in PD. The treatment was complicated by a grade 3 serum amylase and lipase increase and a grade 1 dysphagia.

Then, the patient was candidated for treatment with valemetostat. He was in stage IIIEA (tonsil) at the beginning of the treatment (**Figure 1a**). He received valemetostat 200 mg/day on a continuous 28-day cycle from January to September 2022 for 10 cycles. After 2 cycles, he reached a metabolic CR (**Figure 1b**).

A grade 1 COVID-19 infection complicated the treatment. The first negative swab occurred 1 month after the infection. The patient experienced two episodes of grade 2 E. coli-related urinary tract infection.

In October 2022, the patient underwent allo-SCT, still in CR disease status from a matched unrelated donor (HLA 9/10, for mismatch in A). The washout period between valemetostat and allo-SCT was 14 days. The conditioning regimen consisted of thiotepa, fludarabine, and cyclophosphamide. Acute graft versus host disease (GVHD) prophylaxis consisted of anti-thymocyte globulin, cyclosporine A (CSA), and methotrexate. The neutrophil engraftment occurred at day +12.

The treatment was complicated by Streptococcus mitis-related sepsis. At day +4, veno-occlusive disease was diagnosed, and the patient received defibrotide 6.25 mg/kg/6h for 21 days. At day +20, the patient was diagnosed with engraftment syndrome that required methylprednisolone 2 mg/kg/bid, with the improvement of symptoms. After CSA interruption, the patient experienced a progressive rash that was consistent with GVHD skin 3, gut 0, liver 0, and global 2 that required steroid therapy.

At the last follow-up, the patient was in good clinical condition, and the rash was vanishing. The last restaging, performed 3 months after the allo-SCT, confirmed that the patient is in continuous metabolic CR.

Case #2. In August 2020, a 50-year-old Caucasian woman was diagnosed with PTCL, not otherwise specified, EBV positive, stage IVB for bone marrow and tonsil involvement.

The patient received CHOEP for six cycles from August to November 2020 and 3 lumbar punctures with intrathecal triple therapy (methotrexate, cytarabine, and dexamethasone) as prophylaxis for central nervous system relapse. The patient reached a metabolic CR, but a bone marrow biopsy showed the persistence of lymphoma involvement. Therefore, she received a high dose of cytarabine in January 2021 with hematopoietic stem cell harvesting. A new bone marrow biopsy was still positive for lymphoma involvement.

Then, the patient showed rapid PD with the involvement of the left adrenal gland, rhinopharynx, tonsil, bone marrow, spleen, and soft tissue. Therefore, she was referred to our center where she was treated with AFM-13 for 3 cycles from April to September 2021. After the second cycle, the restaging showed a metabolic CR, and the bone marrow biopsy excluded lymphoma involvement. Therefore, the patient was scheduled for consolidation through allo-SCT, but while the third cycle was ongoing, she experienced a new rapid PD with tonsil and spleen involvement (stage IVsA).

In the absence of another available clinical trial, she was treated with gemcitabine plus oxaliplatin for 3 cycles from October to December 2021, resulting in PD.

Right before valemetostat, the patient showed disease involvement in the tongue, rhinopharynx, and bone marrow (**Figure 2a**).

The patient received valemetostat 200 mg/day for 2 cycles from January to March 2022. After the second cycle, the patient achieved a metabolic CR (**Figure 2b**). A new bone marrow biopsy excluded lymphoma involvement.

The treatment was well tolerated. The first cycle was complicated by the appearance of asymptomatic purpuric skin lesions on the inferior legs and on the right forearm. A skin biopsy showed an inflammatory process.

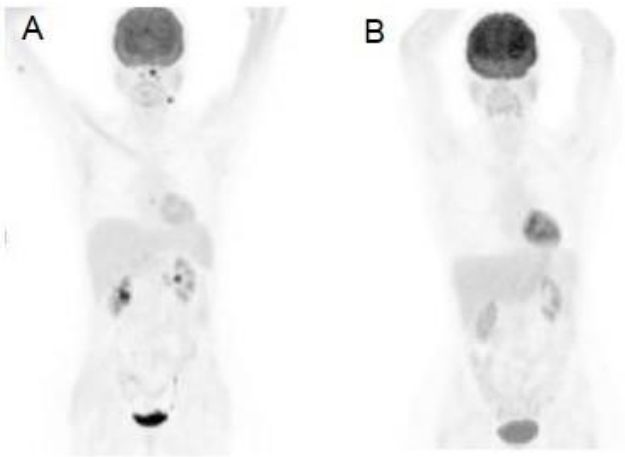

Figure 2. Case 2. Positron Emission Tomography imaging before (**A**) and after (**B**) valemetostat.

The skin lesions resolved after treatment with topic steroid. During the second cycle, a grade 1 dysgeusia occurred.

The patient received haploidentical allo-SCT using her brother as donor. The washout period between valemetostat and allo-SCT was 14 days. The conditioning regimen consisted of thiotepa, busulfan and fludarabine. GVHD prophylaxis consisted of cyclophosphamide on days +3 and +4 and CSA/ mycophenolate mofetil since day +5. The neutrophil engraftment occurred on day 17.

The treatment was complicated by Staphylococcus coagulase negative-related sepsis and pulmonary invasive fungal infection.

At the latest follow-up, the patient was in good clinical condition, and ten months after allo-SCT, she is still in continuous CR.

Discussion. PTCL still retains a poor prognosis, and its management is complicated by the paucity of available effective drugs in the relapsed/refractory setting.

Valemetostat tosylate is a selective dual inhibitor of both wild-type and mutated forms of EZH1 and EZH2. EZH1 and EZH2 are enzymatically active core subunits of polycomb repressive complex 2 (PRC2) that, by the trimethylation of the 27th lysine of histone 3 (H3K27me3), lead to chromatin folding and repression of genes involved in tumor suppression and cell growth.[6-10] By EZH1/2 inhibition, valemetostat leads to chromatin unfolding and unleashing transcriptional expression of these genes.[11]

Valemetostat was recently approved in Japan for treating R/R adult T-cell leukemia/lymphoma (ATL) based on the results of a multicenter phase 2 Japanese trial.[7,12] In this study, 25 patients with R/R ATL received valemetostat 200 mg/die orally until the progression of disease or drug intolerance. The overall response rate (ORR) was 48% (CR rate 20%). The median time to respond was 1.4 months. The most common grade ≥3 adverse events (AEs) were hematological toxicities: thrombocytopenia (32%) and anemia (32%).[7] Valemetostat also showed promising efficacy in a subset of 14 patients with R/R ATL and 45 patients with R/R PTCL in the US and Japanese phase 1 trial in R/R NHL where the ORR was 55.6% (CR rate 24.4%) and 50% (CR rate 21.4%), respectively. The median response time was 8.14 weeks in both subsets.[8]

Valemetostat is currently under clinical evaluation for patients with R/R PTCL in the VALENTINE-PTCL01 trial (NCT04703192).

To our knowledge, no published data about allo-SCT following valemetostat treatment exists. Indeed, no patient in the phase 2 Japanese trial underwent allo-SCT as consolidation after response with valemetostat.

Conclusions. In our patients, valemetostat showed great rapid activity and was well tolerated without significant AEs, leading to consolidation therapy through allo-SCT. Valemetostat is a promising option as bridge therapy to allo-SCT for patients with R/R PTCL, which is still an unmet medical need. Further data are required to understand how valemetostat would affect outcomes of subsequent allo-SCT.

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