Cyclosporine A and Reduced-intensity Conditioning Allogeneic Stem Cell Transplantation for Relapsed Angioimmunoblastic T cell Lymphoma with Hemophagocytic Syndrome

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Abstract

No standard therapeutic approaches have so far been established for the treatment of relapsed angioimmunoblastic T-cell lymphoma (AITL), a subtype of non-Hodgkin lymphoma. This case report describes an AITL patient who relapsed with hemophagocytic syndrome (HPS) two months after receiving high-dose chemotherapy (HDCT) supported by autologous peripheral blood stem cell transplantation (PBSCT). The patient was successfully treated with cyclosporine A (CsA) and subsequent allogeneic PBSCT with reduced intensity conditioning regimen (RIST). RIST may deserve consideration for treatment of AITL patients with severe complications such as HPS. Additionally, CsA could be a less-toxic therapeutic option for pre-RIST induction therapy against AITL.

Key words: angioimmunoblastic T cell lymphoma, cyclosporine A, RIST, hemophagocytic syndrome

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare subtype of non-Hodgkin lymphoma (NHL) that accounts for approximately 2% of all cases of NHL. AITL is frequently accompanied by progressive systemic symptoms such as high fever, body weight loss or night sweating and is also sometimes complicated with severe abnormal immunological symptoms. Among these various symptoms, hemophagocytic syndrome (HPS) is a life-threatening systemic complication of AITL. Although the precise mechanism remains unverified, it has been speculated that functionally activated AITL lymphoma cells generate various cytokines and chemokines that further promote lymphoma cell proliferation in an autocrine and paracrine manner, thereby causing systemic complications (1). Regarding therapy for AITL, conventional anthracycline-based cytotoxic chemotherapies such as the cyclophosphamide, hydroxydaunorubicin, vincristine and predonisolone (CHOP) regimen have been used as first-line treatments; however, a high incidence of relapse has been reported, even in patients who achieve complete remission (CR) with a first-line treatment. Unfortunately, so far, no standard therapeutic approaches have been established for treating relapsed AITL. New therapies are needed for patients who relapse shortly after undergoing intensive chemotherapies, including high-dose chemotherapy (HDCT) supported by autologous peripheral blood stem cell transplantation (aPBSCT). This case report describes the favorable treatment outcome achieved in an AITL patient who relapsed with HPS two months after undergoing HDCT/aPBSCT. The patient was successfully treated with CsA for AITL and subsequent allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning regimen (RIST) as an alternative treatment.

Case Report

A 58-year-old woman was admitted to our hospital with complaints of pharyngeal pain, systemic lymphadenopathy,
splenomegaly and high fever from which she had been suffering for three months. A blood examination revealed an elevated leukocyte count (9.0×10^9/L) and anemia (hemoglobin concentration: 9.7 g/dL). A serological examination showed the presence of polyclonal gammopathy (immunoglobulin (Ig) G: 20.54 g/L, IgM: 2.84 g/L) and elevated levels of soluble interleukin (IL)-2 receptor (9,990 U/mL) and total bilirubin (24.0 mg/dL). Polymerase chain reaction did not detect any Epstein-Barr virus (EBV) DNA in the sera. A computed tomography (CT) scan showed swelling of multiple superficial and mediastinal lymph nodes and subcutaneous tumors that were positive for fluorodeoxyglucose positron emission tomography (FDG-PET) (Figure). A biopsy of the right cervical subcutaneous tumor led to a diagnosis of AITL. An immunohistochemical study revealed that the lymphoma cells were positive for CD3, CD5, CD8 and CD10 and weakly positive for CD4. An in-situ hybridization study revealed that the lymphoma cells were negative for EBV-encoded small RNA. Southern blot analyses disclosed rearrangements of T-cell receptor beta and gamma genes in the cervical tumor sample; however, no bone marrow (BM) invasion was observed. The patient’s disease stage was classified as IVs according to the Ann Arbor staging system.

For the salvage treatment of relapsed AITL in conjunction with G-CSF-mobilized peripheral blood stem cells containing 1.72×10^6 cells/kg of CD34-positive cells were transplanted from an HLA-identical sibling. Neutrophil engraftment was attained on day 15, and the patient achieved a CR for both AITL and HPS. She was discharged 72 days after undergoing allogeneic PBSCT without any evidence of regimen-related toxicity. At present, a CR has been maintained with CsA maintenance therapy (50 mg/day) for 16 months after allogeneic PBSCT without any symptoms of graft-versus-host disease (GVHD).

**Discussion**

Shortly after the initial aPBSCT treatment, three serious problems arose simultaneously: relapse of AITL, post-aPBSCT engraftment failure and HPS, probably accompanied by AITL. Although engraftment failure is a rare complication of aPBSCT, we attribute it at least partly to HPS. For the salvage treatment of relapsed AITL in conjunction with G-CSF- and transfusion-dependent severe pancytopenia due to HPS, we first selected CsA to avoid myelosuppressive adverse events that may result from conventional cytotoxic salvage chemotherapies and to achieve a good performance status for the patient. CsA reportedly has therapeutic potential for both chemotherapy-resistant AITL and HPS without inducing direct adverse effects on hematopoiesis (3-7). The precise mechanism accounting for the efficacy of CsA in treating AITL remains unclear; however, it has been speculated that CsA exerts an anti-lymphoma effect through its direct anti-tumor effect by inhibiting the calcineurin-nuclear factor of activated T-cells (NFAT) transcription factor pathway and shutting down cytokine storms induced by AITL (7). In our case, as was reported, CsA was indeed effective for AITL that relapsed shortly after HDCT, as the systemic tumors regressed within one week. However, CsA was unexpectedly not effective for HPS. Although AITL might be causative for HPS, we speculated that the
treatment of HPS failed because once phagocytes had been excessively activated, the autocrine and paracrine activation of phagocytes could no longer be controlled with CsA alone. In fact, HPS proved to be uncontrollable even with more intensive treatment using etoposide in accordance with the HLH-2004 protocol (2). Under these circumstances, allogeneic stem cell transplantation seemed to be the only option for a curative strategy. RIST, in particular, has the potential to cure ALTL due to the graft-versus-lymphoma (GVL) effect, and can treat HPS by inhibiting phagocytic activity and reconstituting hematopoiesis (8-12). Because our patient did not show any symptoms of GVHD, we cannot be sure whether a GVL effect actually occurred. Therefore, we have been continuing CsA maintenance therapy to avoid re-relapse of AITL. In conclusion, our case suggests that RIST deserves consideration for treatment of patients with AITL with severe complications such as HPS. For pre-RIST induction therapy, CsA is a therapeutic option, as it rarely impairs the patient’s condition.

The authors state that they have no Conflict of Interest (COI).

References