Case report

Long-term remission of primary refractory ALK-positive anaplastic large cell lymphoma after allogeneic hematopoietic stem cell transplantation

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ALK-positive anaplastic large cell lymphoma (ALK+ ALCL) has a favorable prognosis in general; however, some cases are resistant to chemotherapy, which leads to a poor clinical outcome. We herein report the case of a 32-year-old male with aggressive ALK+ ALCL who presented with hemorrhage from a large tumor in the duodenum and multiple tumors in the lungs, mediastinum, and peritoneal cavity. Although induction chemotherapy resulted in a marked reduction of the tumor lesions, premature progression with massive pulmonary infiltration and central nervous system invasion occurred immediately after the completion of chemotherapy. The patient was then promptly treated with brentuximab vedotin (BV) and high-dose methotrexate, which resulted in complete remission. Subsequently, he successfully underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an unrelated donor and has been healthy and did not relapse for more than 3 years after transplantation without any additional therapy. Allo-HSCT may be a promising treatment option for ALK+ ALCL due to its graft-versus-lymphoma effect. In addition, molecular targeting agents, such as BV, may be promising as a bridging therapy before allo-HSCT to achieve disease remission.

Keywords: ALK-positive anaplastic large cell lymphoma, refractory peripheral T-cell lymphoma, brentuximab vedotin, allogeneic hematopoietic stem cell transplantation, graft-versus-lymphoma effect

INTRODUCTION

ALK-positive anaplastic large cell lymphoma (ALK+ ALCL) is a relatively rare but aggressive subtype of peripheral T-cell lymphoma (PTCL), which is highly responsive to chemotherapy and generally has a good prognosis.1 However, in some cases, it is resistant to chemotherapy, resulting in a poor clinical outcome. A treatment strategy for relapsed and refractory ALK+ ALCL has not yet been established. Molecular targeting agents have been reported to be promising for the management of relapsed and refractory ALK+ ALCL; however, they are not necessarily curative. Prolonged disease-free survival after allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been reported in pediatric cases of relapsed and refractory ALK+ ALCL;2,3 however, it remains unknown whether allo-HSCT can be performed in adult patients. Here, we present a case of refractory ALK+ ALCL in an adult in which allo-HSCT after the achievement of complete response (CR) with brentuximab vedotin resulted in long-term relapse-free survival. The findings obtained in this case suggest allo-HSCT may be a promising treatment strategy for relapsed and refractory ALK+ ALCL.

CASE REPORT

A 32-year-old man with no particular medical history presented with a 2-week history of epigastralgia with melena, which resulted in weight loss (5 kg in a month). He was emergently admitted to our hospital because of massive hematemesis. On admission, he had a fever and tachycardia. The complete blood count indicated leukoerythroblastosis (white blood cell count: 17.2 × 10⁹/L; neutrophils, 76%; lymphocytes, 14%; monocytes, 7%; eosinophils, 1%; basophils, 0%; myelocytes, 1%; metamyelocytes, 1%; nucleated red blood cells, 2 of 100 white blood cells) and severe anemia (hemoglobin level, 5.2 g/dL). His platelet count was normal. Biochemical examination showed an increased level of...
C-reactive protein (CRP, 4.58 mg/dL) and a marked elevation in the level of soluble interleukin-2 receptor (sIL-2R, 60,661 U/mL). The lactate dehydrogenase levels were not elevated (153 U/L). Endoscopy showed oozing hemorrhage from a giant tumor at the duodenal bulb. Computed tomography (CT) revealed multiple tumors in both lungs, the mediastinum, and peritoneal cavity. Positron emission tomography revealed marked fluorodeoxyglucose uptake in the tumors (maximal standard uptake value: 35), as indicated by CT (Figure 1a, b). CT-guided biopsy of the lung tumor was urgently performed, and analysis of the biopsied sample showed massive proliferation of abnormal cells with enlarged nuclei and eosinophilic areas (Figure 2a). Immunohistochemistry showed the cells were CD2+, CD3–/+, CD5–, CD7–/+, CD4+, CD8+, CD20+, CD79a+, CD10+, CD56+, CD30+, and ALK+ (Figure 2b–d). The Ki-67 index was >90% (Figure 2e). Epstein-Barr virus-encoded small RNA in situ hybridization was negative. Fluorescence in situ hybridization revealed ALK gene split. Based on the above results, the patient was diagnosed with ALK+ ALCL, and the clinical stage was determined to be IV-B. The international prognostic index (IPI) was evaluated as being high-intermediate risk.

The patient’s clinical course is shown in Figure 3. He was promptly treated with the EPOCH regimen (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin hydrochloride), which markedly improved his general status and decreased the CRP and sIL-2R levels. CT performed after the first chemotherapy course showed a marked decrease in the tumor lesions including the duodenal tumor. Thereafter, the patient was treated with a total of six courses of the EPOCH regimen, and he did not show disease progression. However, a complete response could not be achieved because a small residual lesion was found in the mediastinum a few weeks after the last chemotherapy course. The number of mediastinal lesions rapidly increased within a month (Figure 1c) and caused an elevated inflammatory response and severe respiratory distress. CT revealed diffuse infiltration and spread of mass lesions in both the lungs (Figure 1d). Furthermore, the patient complained of pain behind the left eye. Magnetic resonance imaging showed a mass lesion in the left medial orbit (Figure 1e). Spinal tap revealed an increase in abnormal lymphocytes in the cerebrospinal fluid,
which were suspected to be lymphoma cells based on the cytology results. These findings indicated the progression of ALK+ ALCL.

The patient’s respiratory condition rapidly improved with the administration of pulsed methylprednisolone (mPSL) followed by brentuximab vedotin (BV, 1.8 mg/kg). Intravenous high-dose methotrexate (HD-MTX, 3500 mg/m²) combined with intrathecal (IT) chemotherapy using low-dose MTX was also performed, which resulted in the disappearance of the abnormal cells in the cerebrospinal fluid and the orbital mass. The patient was treated with BV and HD-MTX alternatively, and CR was confirmed after the fourth course of BV. Subsequently, he underwent allo-HSCT from an unrelated donor; it was preceded by the administration of a conditioning regimen comprising fludarabine (180 mg/m²), melphalan (140 mg/m²), cytarabine (8000 mg/m²), and total body irradiation (4 Gy in two fractions). Mismatch of the human leukocyte antigen (HLA) of the graft alleles was noted at one of the eight loci (HLA-DRB1) in both the graft-versus-host and host-versus-graft directions. The prophylaxis for graft-versus-host disease (GVHD) consisted of tacrolimus, anti-thymocyte globulin, and mPSL. The clinical course after transplantation was uneventful, without severe regimen-related toxicities or acute GVHD. Neutrophil engraftment was established on day 11, and complete donor chimerism of the peripheral blood was confirmed. Tacrolimus and steroids were tapered gradually because chronic GVHD was limited to the skin. They were discontinued about 3 years and 2 years, respectively, after allo-HSCT was performed. The patient has been healthy with no signs of lymphoma relapse for more than 3 years after transplantation without any additional therapy.

**DISCUSSION**

ALK+ ALCL is a relatively rare variant of non-Hodgkin’s lymphoma. It is often diagnosed at an advanced stage but has a relatively good prognosis because it is highly responsive to chemotherapy including anthracyclines. ALK+ ALCL is common in children but can also develop in young adults. The 5-year overall survival (OS) and progression-free survival (PFS) rates in both children and adults with ALK+ ALCL have been reported to be 70–90% and 60–80%, respectively. However, some factors influencing a poor prognosis have been reported such as a high IPI and the small cell variant of ALCL. Notably, ALCL patients with a high IPI score (no less than 3) have a significantly poorer prognosis than those with a low IPI score (no more than 2). The prognosis is poor in patients with relapsed ALCL as well, and the survival time after relapse has been reported to be less than 6 months. In such cases, the interval between the initial diagnosis and relapse is a major factor that contributes to a poor prognosis. The prognosis is also substantially poor in cases of ALK+ ALCL wherein the central nervous system (CNS) was involved at the time of relapse. In the present case, the patient was considered to have an extremely poor prognosis considering the high IPI score, premature relapse after the initial treatment, and CNS involvement.

There are various therapeutic strategies for refractory ALK+ ALCL, such as molecular targeting agents, high-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT), and allo-HSCT. Molecular targeting agents, such as BV and ALK inhibitors, have been reported to be highly effective for tumor reduction; however, they have not been found to be curative. A retrospective analysis of 65 patients with relapsed and refractory ALK+ ALCL who underwent HDT/ASCT showed that the 3-year PFS rate was 64%, suggesting that HDT/ASCT may allow long-term disease-free survival in some patients. On the other hand, some analyses of patients with PTCL showed that patients with high IPI scores at the time of diagnosis had a poor prognosis after HDT/ASCT. Allo-HSCT may also be a promising treatment option for achieving long-term remission in refractory cases of various types of PTCL, which was considered to be dependent on the relevant graft-versus-lymphoma effect after allografting in PTCL patients. Although
the superiority of allo-HSCT to HDT/ASCT has not been clarified owing to the high rate of transplant-related mortality associated with it, a recent systematic review and meta-analysis comparing allo-HSCT and HDT/ASCT for PTCL showed that allo-HSCT was associated with specific survival benefits among patients with relapsed/refractory PTCL. Reduced-intensity conditioning is the preferred standard-of-care as the treatment-related mortality after allo-HSCT with myeloablative conditioning for PTCL is very high.

Allo-HSCT for relapsed and refractory ALCL in children has been reported to have good results, with the 5-year disease-free survival rate being 50–60%.[2,3] However, the clinical outcome in adults has been scarcely reported. In an analysis of eight patients aged 9 to 29 years who underwent allo-HSCT with reduced-intensity conditioning for refractory ALCL, sustained disease-free remission was achieved in all cases.[4] Sustained remission of gammadelta T-cell lymphoma by graft-versus-T-cell lymphoma effect. Biol Blood Marrow Transplant. 2018; 30: 2190-2196.

In summary, we present a case of refractory ALK+ ALCL in which long-term survival was achieved after allo-HSCT following disease control with BV. Although further accumulation of clinical experience is required to establish the optimal treatment strategy for refractory ALCL cases in adults, allo-HSCT after bridging therapy with molecular targeting agents may be a promising treatment option for such cases.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest relevant to this study.

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