Cyclosporine Treatment of Angioimmunoblastic T-Cell Lymphoma Relapsed After an Autologous Hematopoietic Stem Cell Transplant

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Abstract

An angioimmunoblastic T-cell lymphoma is a unique type of peripheral T-cell lymphoma; it has an aggressive course and a poor prognosis. There is no standard therapy for angioimmunoblastic T-cell lymphoma, especially for refractory or relapsed cases. Here, we report a case of 53-year-old woman with angioimmunoblastic T-cell lymphoma who underwent high-dose chemotherapy with an autologous hematopoietic stem cell transplant after several cycles of chemotherapy, but soon relapsed with severe autoimmune hemolytic anemia. The patient was given dexamethasone and thalidomide, but responded poorly; however, she responded well to cyclosporine and finally achieved a sustained response. Thus, we conclude that cyclosporine has an effect in relapsed angioimmunoblastic T-cell lymphoma after an autologous hematopoietic stem cell transplant.

Key words: Peripheral T-cell lymphoma, Relapse, Therapy

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma characterized morphologically by lymphadenopathy with polymorphic infiltrate, marked vascular, and follicular dendritic cell proliferation.1,2 Patients usually present with advanced disease with a polyclonal gammopathy and features of immune dysregulation. The diagnosis of AITL is based on a lymph node biopsy. Further treatment of this lymphoma is difficult. Disease outcomes remain worse than more common types of high-grade lymphomas. More recently, there have been several reports of successful therapy of refractory AITL using thalidomide and dexamethasone.3-5 No better strategy has been found for patients that do not respond to these drugs, especially cases that have relapsed from autologous hematopoietic stem cell transplant (A-HSCT).

Here, we report a case of AITL in a woman who was refractory and relapsed after A-HSCT but achieved a remarkable sustained response to treatment with cyclosporine and bevacizumab when she had failed to respond to thalidomide and dexamethasone.

Case Report

A 53-year-old woman presented with fast-growing superficial lymph nodes of the body and fatigue of 1 month’s duration in May 2010. A physical examination found pale complexion and neck lymph node enlargement, without liver and spleen enlargement. She had a high lactate dehydrogenase, hyperimmunoglobulinemia, a reversed kappa-to-lambda ratio of 0.65, and an elevated level of Epstein-Barr virus DNA in the blood. Routine blood tests showed pancytopenia (white blood cell count, 1.19 × 10^9/L; red blood cell count, 2.43 × 10^12/L; hemoglobin, 76 g/L; platelets, 46 × 10^9/L). Biopsies from cervical lymph nodes finally revealed AITL (Figure 1), stage IVB. A bone marrow aspiration smear showed a slightly hypocellular marrow.
She received chemotherapy with a cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone (CHOP) regimen for 4 cycles, with partial improvement of superficial lymph node enlargement and pancytopenia. A positron emission tomography/computed tomography examination of her body revealed that the primary lesions presented as a space-occupying with condensed radioactivity. The mean maximal standard uptake value (SUVmax) was 11.6 ± 5.3. Her disease progressed, as shown by enlarginginguinal lymph nodes on physical examination and a small amount of lymphoma cells on a bone marrow smear. Second-line treatment with fludarabine, mitoxantrone, dexamethasone was used for 2 cycles, with additional intrathecal methotrexate, cytarabine, and dexamethasone for leukemia prophylaxis of the central nervous system. Superficial lymph nodes could not be palpated, and hemoglobin and platelet levels were restored. Furthermore, she received an autologous hematopoietic stem cell transplant, with a conditioning regimen composed of lomustine, cytarabine, cyclophosphamide, and etoposide. She received mononuclear cells (10.8 × 10^8/kg). The transplant and hematopoietic reconstitution went well.

After 3 months of disease stabilization, a progression in cervical, distant lymph nodes, and severe anemia were observed. A bone marrow examination found a small amount of lymphoma cells, and the immunohistochemical staining showed these were from T cells. The diagnosis of relapsed AITL with autoimmune hemolytic anemia was made. She then started taking daily oral thalidomide (100 mg) and dexamethasone (15 mg) for 4 weeks. No response was achieved. Refractory diarrhea and fever occurred. Beginning in October 2011, she was given cyclosporine (125 mg orally twice daily) and the monoclonal vascular endothelial growth factor antibody, bevacizumab (5 mg/kg every week for 3 doses). After 1 week, her condition improved. After 4 weeks, we noted a disappearance of enlarged lymph nodes, as assessed with a B-ultrasound and computed tomography scan. Meanwhile, her hemoglobin level rose to normal level (Table 1). Cyclosporine (50 mg orally twice daily) was given for maintenance treatment. The patient’s quality of life was excellent, lasting for more than 18 months.

**Discussion**

Angioimmunoblastic T-cell lymphoma was described initially as angioimmunoblastic lymphadenopathy by Frizzera and associates in the early 1970s. Angio-immunoblastic T-cell lymphoma is now recognized as a distinct type of peripheral T-cell lymphoma and was incorporated in the 2008 World Health Organization classification of hematolymphoid neoplasms.6 Angio-immunoblastic T-cell lymphoma

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Diagnosed</th>
<th>Post-HSCT</th>
<th>Relapsed</th>
<th>Dex &amp; Thal</th>
<th>Cyc (1 mo)</th>
<th>Cyc (1 y)</th>
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<tbody>
<tr>
<td>WBC (×10^9/L)</td>
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<td>3.49</td>
<td>2.63</td>
<td>2.53</td>
<td>3.38</td>
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<tr>
<td>Hb (g/L)</td>
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<td>85</td>
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<tr>
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<td>123</td>
<td>86</td>
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<tr>
<td>Lymph nodes</td>
<td>**</td>
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</tr>
<tr>
<td>Symptoms</td>
<td>Fever</td>
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<td>Fatigue</td>
<td>Diarrhea, Fever</td>
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<td>None</td>
</tr>
</tbody>
</table>

*Abbreviations:* Cyc, cyclosporine; Dex & Thal, use of dexamethasone and thalidomide; Hb, hemoglobin; PLT, platelet count; Post-HSCT, after hematopoietic stem cell transplant; WBC, white blood cell count. Lymph nodes showed superficial lymph nodes detected by B ultrasound, ++≥ 2 cm, –≤ 5 mm.
accounts for approximately 1% to 2% of all non-Hodgkin lymphomas with an aggressive course and a poor prognosis, and it tends to occur in adults presenting with systemic symptoms. It is frequently associated with hypergammaglobulinemia and autoimmune features. The prognosis for AITL is poor when compared with other lymphoid disorders. While intensive chemotherapy induces complete remissions in 50% to 70% of patients, most patients subsequently relapse, resulting in a 5-year survival of 30% and a median survival time of only 3 years.

There are no standard treatments for AITL. The clinical effects of these therapies remain controversial. Furthermore, there is a rare report of treatment outcomes for AITL, especially for refractory or relapsed ones after A-HSCT. Different cases were empirically treated based on the clinician’s experience.

Most approaches are extrapolated from management of aggressive B-cell lymphomas. They include therapies for AITL such as chemotherapy, transplant, and immunosuppressions. Angioimmunoblastic T-cell lymphoma shows high levels of vascular endothelial growth factor expression on lymphoma cells and endothelial cells, so anti-angiogenic therapy (eg, bevacizumab) is an attractive treatment. However, anti-angiogenic therapy as a single treatment may not be so effective according to our experience and a report, especially for refractory or relapsed AITL. In the current case, only 3 doses of bevacizumab were used in the second month after relapse from A-HSCT; they were then stopped because of a financial issue. In the same time, immunomodulatory agents (eg, cyclosporine, thalidomide, and dexamethasone) were reported to be effective for some refractory AITL. The current case did not only respond to anti-angiogenic therapy or single immunomodulatory agents (eg, thalidomide and dexamethasone) when relapsed from A-HSCT.

The current case responded to A-HSCT for 3 months. She then had stabilized improvement with cyclosporine for 18 months more. Taken together, the combination of therapeutic strategies including A-HSCT, anti-angiogenic agents, and immunomodulatory agents (ie, immunosuppressive agents) may be considered an optional effective method to treat refractory and relapsed AITL. It deserves further testing as a novel therapy for AITL.

References