

Brentuximab in the Treatment of CD30-Positive Enteropathy-Associated T-Cell Lymphoma

Waleed F. Khalaf, MD; Meghan E. Caldwell, BS, MSN; and Nishitha Reddy, MD, MSCI

Abstract

Enteropathy-associated T-cell lymphoma (EATL) is a rare aggressive lymphoma that confers a poor prognosis with current treatment strategies. Given the rarity of this disease, prospective randomized trials are limited, and thus a standard validated treatment strategy is lacking. This report presents the disease course of a patient with EATL who was treated with single-agent brentuximab vedotin, an anti-CD30 conjugated antibody. (*JNCCN* 2013;11:137–140)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the rationale for the management methods used in this case presentation.
- Describe the ideal management of a patient taking brentuximab for the treatment of CD30-positive enteropathy-associated T-cell lymphoma.

Case Report

A 64-year-old man presented with an acute small bowel obstruction that was preceded by a few months' history of intermittent diarrhea, fever, and weight loss. Pathology of the small bowel resection was consistent with enteropathy-associated T-cell lymphoma (EATL) that expressed CD3 and CD30; was negative for CD4, CD8,

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CD52, and CD56; and showed partial loss of CD5, all in a background pattern consistent with celiac sprue. CT scan revealed mural thickening and multiple enlarged mesenteric lymph nodes, the largest of which measured 1.2 x 3.9 cm, and multiple pulmonary nodules. CBC results showed a normal white count, microcytic anemia with a hemoglobin B level of 12.9 g/dL, a mean corpuscular volume of 76 fL, and thrombocytosis. A complete metabolic profile showed normal values, other than mildly reduced albumin levels at 3.3 g/dL. Results of iron studies were consistent with iron-deficiency anemia.

The patient was subsequently started on combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). After 4 cycles, he was noted to have a partial response on CT imaging. Shortly thereafter, the patient experienced a resurgence of his B symptoms, and subsequent therapy included ifosfamide, carboplatin, and etoposide (ICE), which was complicated by arterial and venous thrombosis and gastrointestinal bleeding. Subsequent endoscopy revealed areas of large ulceration in the terminal ileum, a biopsy of which showed involvement by EATL.

Given his persistent disease, the patient was started on third-line treatment with gemcitabine and vinorelbine. Evaluation after 2 cycles of therapy revealed that he had progressive disease, and therapy thereafter was changed to romidepsin. At best, he had stable disease after 2 cycles of treatment. This therapy, however, was complicated by multiple admissions with neutropenic fever. Two months later, workup during a recurrent hospitalization for fever and acute-onset back pain revealed the presence of a new paraspinal mass and retroperitoneal adenopathy. CT-guided biopsy of the paraspinal mass was suspicious for involvement of his known lymphoma.

Given his B symptoms and progression of disease radiographically, he was started on salvage treatment with brentuximab vedotin (BV), because his lymphoma strongly expressed CD30. BV was administered at a dose of 1.8 mg/m² every 3 weeks. Repeat CT scan after the third cycle showed a remarkable response, with improvement in multiple nodal groups in the retroperitoneum and pulmonary nodules (Figure 1). B symptoms resolved after the first cycle. The dose of BV was reduced to 1.0 mg/m² after 4 cycles because of neuropathy. Complete remission was documented after 8 cycles, and subsequent therapy was stopped.

The patient tolerated BV well, except for grade 3 neuropathy that progressed from his baseline grade 2 neuropathy. He developed mild leukopenia without neutropenia. At his 9-month follow-up, the patient continued to show disease remission.

Discussion

EATL is a rare gastrointestinal lymphoma that accounts for fewer than 1% of all non-Hodgkin's lymphomas, although the incidence seems to be increasing in the United States.¹ Type I EATL is strongly associated with celiac disease and linked to the HLA-DQ2 haplotype. Histologically, these lymphomas are pleomorphic and often express CD30. Most cases of EATL express CD30 on a proportion of tumor cells; in a study of 23 patients with EATL, CD30 was expressed in more than 80% of cases.^{2,3}

As for the treatment of EATL, no validated treatment strategies exist because of the lack of randomized clinical trials. Given the rarity of this disease, only single-institution experiences and retrospective studies are available. The most widely used treatment in clinical practice is anthracycline-based combination chemotherapy, followed by an autologous stem cell transplant (ASCT) in eligible individuals. The overall response rate varies from 30% to 60%, mostly using a CHOP-like regimen.⁴⁻⁹

With current treatment strategies, the median overall survival is 10 months, with an estimated 5-year overall survival of 20%.¹⁰ The most frequent cause of death involves intestinal complications of persistent disease, such as perforation and bleeding. Furthermore, estimates show that up to 50% of patients are unable to undergo chemotherapy because of their poor performance status secondary to malnutrition or intestinal complications associated with their disease.

For most patients in whom first-line treatment with a CHOP-like regimen fails, prognosis is very poor, and limited data exist on second-line therapy. In a retrospective single-center study from Austria, 19 patients were identified with EATL between 1999 and 2010, and only 6 received second-line therapy.¹¹ The regimens used were ICE, FC (fludarabine and cyclophosphamide), DHAP (dexamethasone, cisplatin, and cytarabine), and cladribine. This study highlighted the poor prognosis of EATL, but suggests that a small proportion of patients may benefit from

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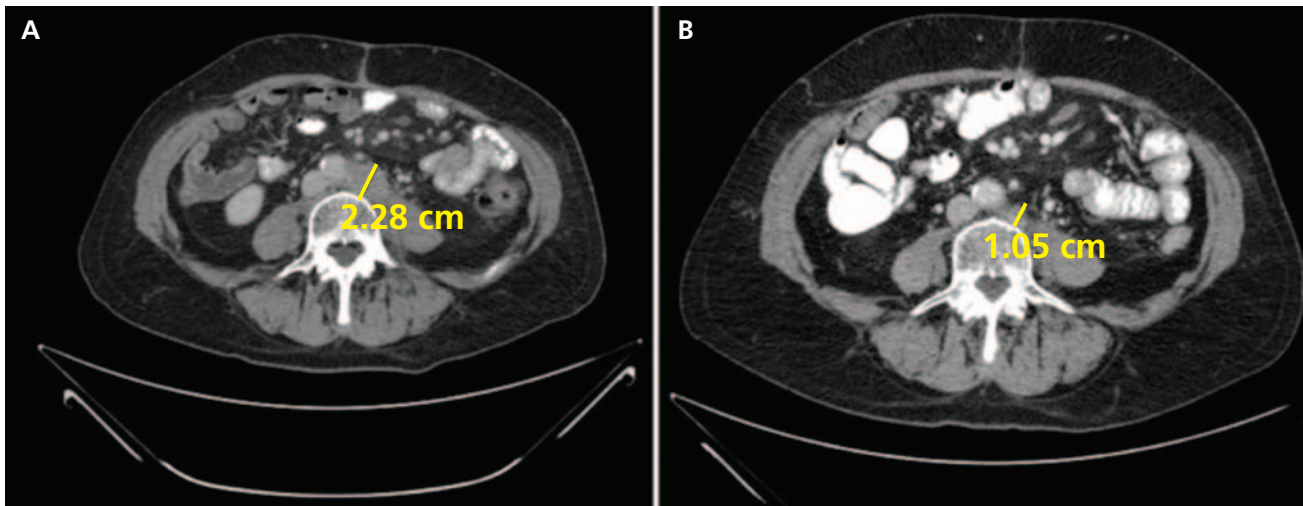


Figure 1 Representative CT images showing para-aortic adenopathy before (A) and after (B) treatment with 3 cycles of brentuximab vedotin.

second-line therapy. The largest trial evaluating the role of ASCT was a prospective study from a population-based setting from the Scotland and Newcastle Lymphoma Group.⁹ In this study, patients who received IVE/MTX (ifosfamide, etoposide, epirubicin, and methotrexate)-ASCT showed improved 5-year progression-free and overall survivals compared with those treated with a CHOP-like regimen (progression-free survival, 52% vs. 22%; overall survival, 60% vs. 22%).

BV is an anti-CD30 chimeric antibody conjugated to the potent antimetabolic agent monomethyl auristatin E (MMAE). After binding to CD30, BV is internalized and transported to lysosomes, where MMAE is cleaved and, once released, will bind to tubulin and cause cell cycle arrest and apoptosis.¹² In the pivotal phase I study, the maximum tolerated dose was 1.8 mg/m² and objective responses were observed in 38% of patients.¹³ In a prospective study of patients with CD30-positive recurrent anaplastic large cell lymphoma, of the 58 patients who were treated with BV, 50 experienced an objective response with 33 complete responses. The median duration of remission was 13.6 months.¹⁴

Theoretically, BV may be beneficial in any CD30-positive lymphoid neoplasm; however, no data seems to be available describing its use or benefit in EATL. The excellent clinical and radiographic response reported in this case highlights the need to further evaluate its role in patients with EATL.

Conclusions

The current NCCN Clinical Practice Guidelines in Oncology recommend using multiagent chemotherapy followed by high-dose therapy and stem cell transplantation for EATL.¹⁵ This regimen should still be the preferred therapy in eligible patients who can tolerate it, because current evidence supports its use. Until further data are available, the authors recommend considering BV in patients who have a poor tolerance of chemotherapy or in the absence of other standard options.

References

1. Sharaiha RZ, Leibold B, Reimers L, et al. Increasing incidence of enteropathy-associated T-cell lymphoma in the United States, 1973-2008. *Cancer* 2012;118:3786-3792.
2. Wright DH. Enteropathy associated T cell lymphoma. *Cancer Surv* 1997;30:249-261.
3. Murray A, Cuevas EC, Jones DB, Wright DH. Study of the immunohistochemistry and T cell clonality of enteropathy-associated T cell lymphoma. *Am J Pathol* 1995;146:509-519.
4. Gale J, Simmonds PD, Mead GM, et al. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. *J Clin Oncol* 2000;18:795-803.
5. Novakovic BJ, Novakovic S, Frkovic-Grazio S. A single-center report on clinical features and treatment response in patients with intestinal T cell non-Hodgkin's lymphomas. *Oncol Rep* 2006;16:191-195.
6. Daum S, Ullrich R, Heise W, et al. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal Non-Hodgkin's Lymphoma. *J Clin Oncol* 2003;21:2740-2746.
7. Egan LJ, Walsh SV, Stevens FM, et al. Celiac-associated lymphoma. A single institution experience of 30 cases in the combination chemotherapy era. *J Clin Gastroenterol* 1995;21:123-129.

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8. Wöhrer S, Chott A, Drach J, et al. Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) is not effective in patients with enteropathy-type intestinal T-cell lymphoma. *Ann Oncol* 2004;15:1680–1683.
9. Sieniawski M, Angamuthu N, Boyd K, et al. Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. *Blood* 2010;115:3664–3670.
10. Delabie J, Holte H, Vose JM, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the International Peripheral T-Cell Lymphoma Project. *Blood* 2011;118:148–155.
11. Raderer M, Troch M, Kiesewetter B, et al. Second line chemotherapy in patients with enteropathy-associated T cell lymphoma: a retrospective single center analysis. *Ann Hematol* 2012;91:57–61.
12. Senter PD, Sievers EL. The discovery and development of brentuximab vedotin for use in relapsed hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Nat Biotechnol* 2012;30:631–637.
13. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010;363:1812–1821.
14. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol* 2012;30:2190–2196.
15. Zelenetz AD, Abramson JS, Advani RH, et al. NCCN Clinical Practice Guidelines in Oncology for Non-Hodgkin's Lymphomas. Version 1.2013. Available at: NCCN.org. Accessed January 16, 2013.

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Posttest Questions

1. True or False: The current NCCN Clinical Practice Guidelines in Oncology recommend using multiagent chemotherapy followed by high-dose therapy and stem cell transplantation for EATL.
2. True or False: No validated treatment strategies exist for the

treatment of EATL because of the lack of randomized clinical trials.

3. True or False: Type I EATL is strongly associated with celiac disease and linked to the HLA-DQ2 haplotype.

