

Bendamustine Induced Neurotoxicity

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Introduction

Bendamustine (Treanda, Cephalon) is a unique compound composed of an alkylating agent (a nitrogen mustard derivative) and a benzimidazole ring (similar to a purine analog).¹ Originally developed in the 1960s, the rationale behind the drug was to use both its anti-metabolite activity and alkylating properties to produce an effective drug with a lower toxicity profile than other alkylating agents.² Currently, bendamustine is approved by the U.S. Food and Drug Administration for the treatment of chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin lymphoma (NHL) refractory to rituximab (Rituxan, Genentech), and its efficacy is being investigated in a number of other histologies of NHL and multiple myeloma. Reported adverse effects have been limited mainly to hematologic and gastrointestinal toxicities.^{3,4} However, purine analogs are known to cause neurotoxicity, which may have a delayed onset.⁵ To date, no known report of neurologic side effects from the use of bendamustine exists in the literature.

Case Report

The patient is a 63-year-old man who was diagnosed with stage IV follicular lymphoma in September 2005. He had previously been healthy, other than the presence of irritable bowel syndrome and Gilbert's syndrome. He was initially treated with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) from November 2005 to March 2006, with a partial response. This therapy was well tolerated, except for mild paresthesias in his fingertips, which later resolved. However, by October 2006, a positron emission tomography/computed tomography (PET-CT) scan showed disease progression. The patient was referred to Georgetown University Hospital, Lombardi Comprehensive Cancer

Center where he was enrolled in a phase II clinical trial evaluating bendamustine in patients with indolent NHL refractory to rituximab. He received 7 cycles of bendamustine from November 2006 to April 2007. Cycles 1–5 were administered at a dose of 120 mg/m² on days 1 and 2 every 3 weeks. He tolerated these cycles well, except for mild, transient peripheral neuropathy after cycle 1. The dose administered during cycles 6–7 was reduced to 90 mg/m² on days 1 and 2 because of anemia.

In June 2007, 2 months after his last cycle of bendamustine, the patient developed lower extremity numbness, which rapidly progressed over 1–2 weeks to include his entire legs, buttocks, and groin, associated with bowel and bladder incontinence, generalized lower extremity weakness, and severe altered mental status. He became paraplegic and unable to function at home, and was admitted to the hospital in late June 2007. He had 2/5 strength bilaterally in his hip flexors, 4/5 strength on ankle dorsiflexion, and 5/5 strength in his upper extremities. The neurologic evaluation was otherwise negative. Magnetic resonance imaging of the spine and brain showed no abnormal enhancement, hemorrhage, ischemia, or cord compression that would account for his symptoms. Cerebrospinal fluid studies were negative and did not show any lymphoma or infectious etiology. B12 and folate levels were normal, and rapid plasma reagin was nonreactive. The patient was treated with intravenous steroids with only slight improvement in his neuropathy. In light of his negative laboratory findings, a side effect from bendamustine was considered the likely etiology of his symptoms. His condition stabilized, and he was discharged to a rehabilitation center on a tapering dose of steroids, but with persistent weakness, incontinence, and neuropathy. In July 2007 he was re-admitted for worsening mobility with weakness. He had bilateral 3/5 strength in his lower extremities, 4/5 strength in the upper extremities, a fine tremor, incontinence, and a sensory neuropathy in his lower extremities. Imaging and cerebrospinal fluid studies were again negative. Of note, CT scans and peripheral blood flow cytometry showed no signs of lymphoma. The patient's immobility was

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impaired such that he developed sacral ulcers. His weakness gradually improved without treatment, but all other symptoms persisted. He was discharged to a rehabilitation center, from which he was sent home in August 2007.

In April 2008, evaluation revealed only minimal clinical improvement, with persistent severe neurologic sequelae, weight loss of greater than 30 pounds, and a significant reduction in his quality of life. He had incontinence that intermittently required an indwelling urine catheter, and he occasionally required a walker for ambulation because of severe lower extremity weakness. A painful peripheral neuropathy persisted in his lower extremities despite treatment with gabapentin. He was able to live at home with assistance, yet had minimal participation in activities of daily living. A neurologic consultation in October 2008 concluded that the patient's symptoms were in all likelihood permanent and he was not going to recover. In May 2009, a computed tomography scan showed persistent mild splenomegaly without lymphadenopathy. His condition continued to slowly improve such that, by August 2009, he had gained back all of his lost weight, the lower extremity neuropathy had lessened, he had regained bowel and bladder control, was walking without assistance, with an ECOG performance status of 1, and he was able to resume previous activities including rifle shooting.

Discussion

Bendamustine is being increasingly used in the treatment of a number of lymphoid malignancies. Although this drug is generally well-tolerated, the present case demonstrates the possibility of severe neurologic sequelae related to its use. Despite extensive investigation, no other etiology could be identified for the neurologic symptoms. Cheson and colleagues reported that purine analogs such as fludarabine, cladribine, and pentostatin produce

neurotoxicity that can be delayed and irreversible.⁵ The mechanism of such toxicity is unclear. Higher doses of these drugs and age greater than 60 years were risk factors for purine analog-associated neurotoxicity. Yet, 85% of the neurologic effects related to fludarabine, cladribine, and pentostatin were mild to moderate and transient. Thus, it is unusual to encounter severe neurotoxicity from purine analogs that significantly impacts quality of life as in the present case.⁵ Whether the mild neuropathy the patient experienced after the first cycle was predictive of later neurotoxicity is unknown. Therefore, bendamustine may be associated with delayed neurotoxicity with a clinical picture similar to purine analogs. No significant neurotoxicity has been reported with bendamustine despite thousands of patients treated in the German Democratic Republic over the past 40 years. Nevertheless, as an increasing number of patients are treated with this agent in the United States, and with the anticipated European approval, enhanced surveillance may identify more cases of this and other rare side effects. Thus, reports of rare adverse effects are essential to alert the treating physician to their possibility.

Conflicts of Interest: Dr. Cheson reports serving on an advisory board for Cephalon.

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Review

What Causes Neurotoxicity After Exposure to Purine Analogs?

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Bendamustine was synthesized in 1962, but did not become available in the United States until 2008, when it was approved by the U.S Food and Drug Administration (FDA) for the treatment of chronic lymphocytic leukemia (CLL). However, relatively little data were generated describing the clinical activity and toxicity of bendamustine between 1962 and 2008. As a result, lack of both clinical experience and published data confuses the proper role of bendamustine in the treatment of low-grade lymphoproliferative disorders.

Recently, data were generated by 3 clinical trials designed for the treatment of indolent B-cell non-Hodgkin lymphoma (NHL). In the first trial, 77 patients with NHL refractory to rituximab (Rituxan, Genentech) were treated with bendamustine (Treanda, Cephalon) 120 mg/m² on 2 consecutive days every 21 days. The overall response rate (ORR) was 77%, and 34% achieved complete remission (CR).¹ In the other 2 trials, a total of 130 patients with relapsed and refractory NHL were treated with rituximab 375 mg/m² on day 1 and bendamustine 90 mg/m² on days 2 and 3 of a 28-day treatment cycle. Rituximab was also infused 1 week before the first treatment cycle and 4 weeks after the fourth and final treatment cycle. The ORR was 90% in 1 trial and 92% in the other, with a corresponding CR rate of 60% and 55%, respectively.^{2,3} These results led to the approval of bendamustine for the treatment of indolent B-cell lymphomas by the FDA.

As important as these impressive responsive rates are, the toxicity encountered in all 3 trials was relatively modest. Hematologic toxicity was common, with grade 3/4 leukopenia in 16–30% of patients depending on the

system used to grade toxicity. Although nonhematologic toxicities were common, they were generally mild with grade 1/2 nausea in 68% and grade 1/2 fatigue in 42% of patients. Alopecia and mucositis are uncommon with bendamustine. To date, only mild neurotoxicity has been described. In a phase II trial of bendamustine for treatment of relapsed soft tissue sarcomas, 4 of 36 patients (11%) developed grade 1/2 peripheral neuropathy, not otherwise specified.⁴ A case of mild hypacusis and another of paresthesia were described in a phase I/II study of bendamustine monotherapy for relapsed CLL, but these toxicities might have been related to pre-existing comorbid disease.⁵

Drs. Cheson and Kroll report a severe neurologic syndrome that developed 2 months following the completion of a successful course of single-agent bendamustine in a patient with follicular NHL.⁶ They describe a paralysis that occurred over several weeks despite treatment with steroids. Although mechanical ventilation was not required, bowel and bladder dysfunction complicated the clinical picture, and the syndrome took nearly 2 years to resolve.

Bendamustine may have been the cause of the neurologic damage. As Drs. Cheson and Kroll point out, purine analogs have been implicated as the cause of delayed onset neurotoxicity,⁷ and bendamustine shares a benzimidazole ring structure similar to the other purine analogs. If confirmed, the observations of Drs. Cheson and Kroll would not only point out a previously unknown toxicity, but would also be the first evidence that bendamustine really does have a purine analog function that its structure suggests.

However, the mechanism of purine analog-associated neurotoxicity is unknown and may not be due to the presence of a benzimidazole structure. Benzimidazole antifungal agents, like albendazole, are not known to be neurotoxic.⁸ Perhaps the neurotoxicity is indirect and results from the immunosuppression that these agents cause. Data from an unpublished study by Dr. Wendtner of bendamustine combined with rituximab in relapsed CLL show a prolonged decrease of CD4+ T-cell counts similar to that which occurs after treatment with fludarabine.

Acute inflammatory demyelinating polyneuropathy (AIDP) often follows an infectious insult.⁹ The neurologic syndrome experienced by the patient described by Drs. Cheson and Kroll bears features similar to AIDP, including ascending paralysis, symmetry, and the absence of fever. Whether or not the patient was areflexic is unclear from the text. The cerebrospinal fluid studies are not described in detail, nor are any electrodiagnostic studies. The bowel and bladder dysfunction and the progression of symptoms over approximately

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8 weeks are unusual with AIDP, but do not rule out the diagnosis.

Although the case presentation is not conclusive that bendamustine directly caused the patient's paralysis, the association with bendamustine treatment is convincing. This case demonstrates the vigilance required when investigating new drugs and cautions against the use of these agents outside the context of a clinical trial in situations where they have not been previously explored.

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