

# Safe and Effective Treatment of Aggressive Non-Hodgkin Lymphoma With Rituximab and Bendamustine in Patients With Severe Liver Impairment

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## Introduction

Rituximab (Rituxan, Genentech/Biogen Idec Pharmaceuticals) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is currently the most widely used first-line therapy for aggressive B-cell lymphomas.<sup>1</sup> However, many patients, including those with organ dysfunction, may not tolerate the toxicities associated with this regimen. Recent data from the phase III Study Group Indolent Lymphomas (StiL) non-Hodgkin lymphoma (NHL)-1 trial suggested that bendamustine (Treanda, Cephalon) plus rituximab was superior in effectiveness and tolerability compared to R-CHOP in the treatment of indolent and mantle cell lymphomas.<sup>2</sup> Small studies have indicated the effective use of bendamustine alone or in combination in the treatment of aggressive B-cell lymphomas as well.<sup>3-5</sup> Here we report the safe and effective use of bendamustine plus rituximab in 2 patients: one patient with transformation from follicular lymphoma to diffuse large B-cell lymphoma (DLBCL), and another patient with de novo DLBCL. Both patients had severe liver impairment. They tolerated treatment without adverse effects and had a dramatic initial response.

## Case 1

Mr. S. is a 51-year-old African American jazz vocalist who was discovered to have a large mediastinal mass in 2001 after a routine pre-employment chest x-ray and subsequent biopsy made the diagnosis of follicular lymphoma earlier

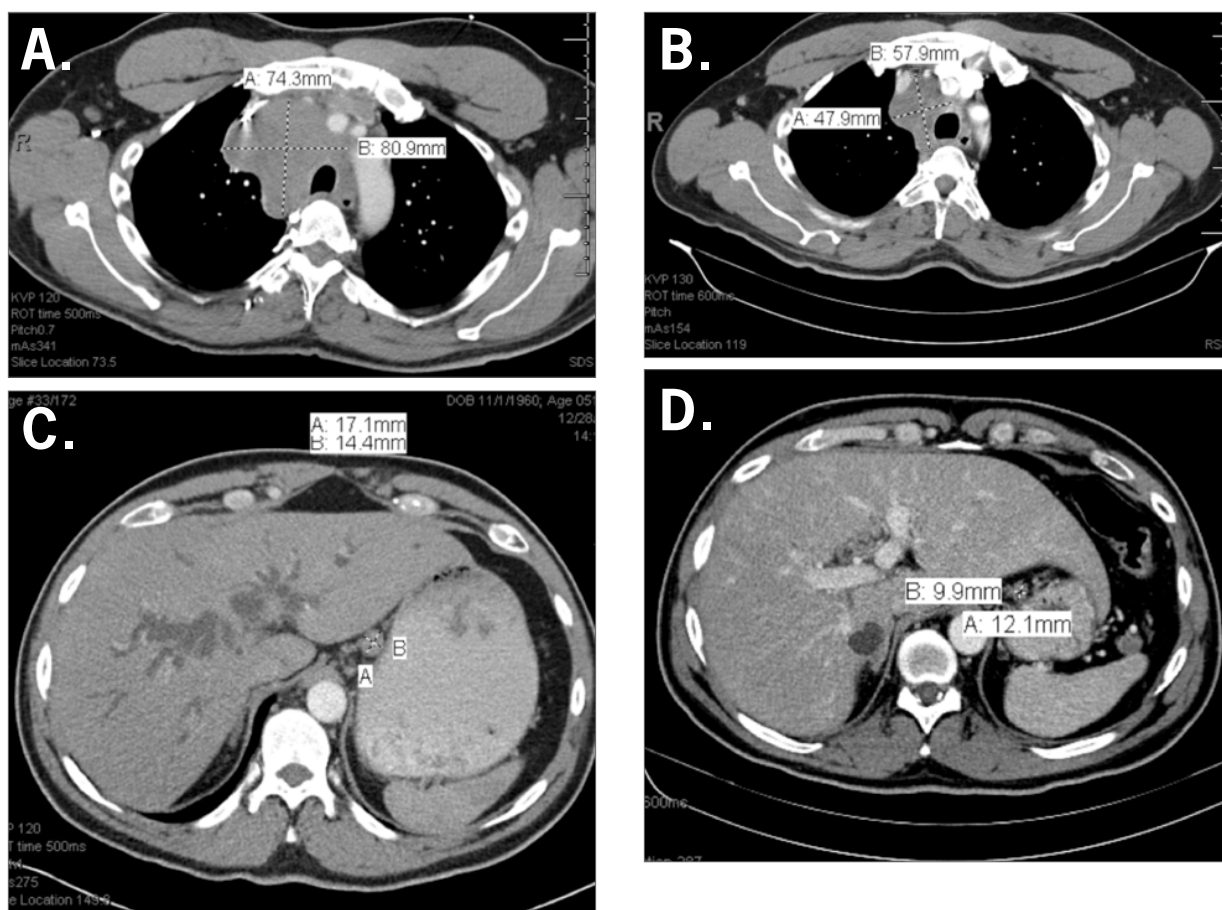
that year. A watch-and-wait approach was taken until 2004, when he developed worsening adenopathy. He was treated by his local oncologist with 8 cycles of rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). The patient had a reported partial response, but with a persistent mediastinal mass.

The patient did well on continued active surveillance until late December 2011, when he presented with hoarseness and obstructive jaundice, with a total serum bilirubin of 23.4 mg/dL (reference range, .2–1.2 mg/dL). Alanine transaminase (ALT) and aspartate transaminase (AST) levels were mildly elevated, at 93 mg/dL (6–33 mg/dL) and 74 mg/dL (8–40 mg/dL), respectively. Alkaline phosphatase was 617 mg/dL (43–130 mg/dL) and lactate dehydrogenase (LDH) was 452 mg/dL (3.9–5.2 mg/dL). A computed tomography (CT) scan of the abdomen showed new retroperitoneal and mesenteric adenopathy. Diffuse intrahepatic and extrahepatic biliary dilatation was noted with an obstructing ampullary mass adjacent to the pancreatic head. CT of the neck and chest revealed a large right mediastinal mass involving the right laryngeal nerve. Laryngoscopy confirmed right vocal cord paralysis.

On January 3, 2012, bronchoscopy and endobronchial ultrasound with mediastinal lymph node biopsy, and esophagogastroduodenoscopy with ultrasound and biopsy of the ampullary mass were performed. Tissue from both sites was consistent with a germinal cell–like large B-cell lymphoma, which was likely a transformation from his prior follicular NHL. Subsequent bone marrow biopsy showed no evidence of lymphoma. Staging positron emission tomography (PET)-CT on January 9 revealed extensive lymphadenopathy in the mediastinal, right axillary, and right supraclavicular regions. A hypermetabolic ampullary mass and extensive peripancreatic and perigastric lymphadenopathy demonstrated increased standardized uptake value (SUV) activity.

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**Figure 1.** Radiographic response in Mr. S. following 1 cycle of rituximab and bendamustine. A) Pretreatment chest computed tomography (CT) scan demonstrating mediastinal mass measuring 74.3 mm × 80.9 mm. B) Day 28 chest CT showing the mediastinal mass that decreased in size to 57.9 mm × 47.9 mm. C) Pretreatment abdominal CT with abdominal adenopathy and intrahepatic ductal dilation. D) Day 28 abdominal CT showing decreased size of abdominal lymph nodes and improved intrahepatic ductal dilatation.

Therapy with R-CHOP was initially considered; however, given the patient's severe liver dysfunction, the dose of both doxorubicin and vincristine would need to be significantly reduced. Moreover, given his previous exposure to R-CVP that resulted in only a modest response, the decision was made to treat the patient with rituximab 375 mg/m<sup>2</sup> on day 1, and bendamustine 90 mg/m<sup>2</sup> on days 1 and 2 during this initial hospitalization.

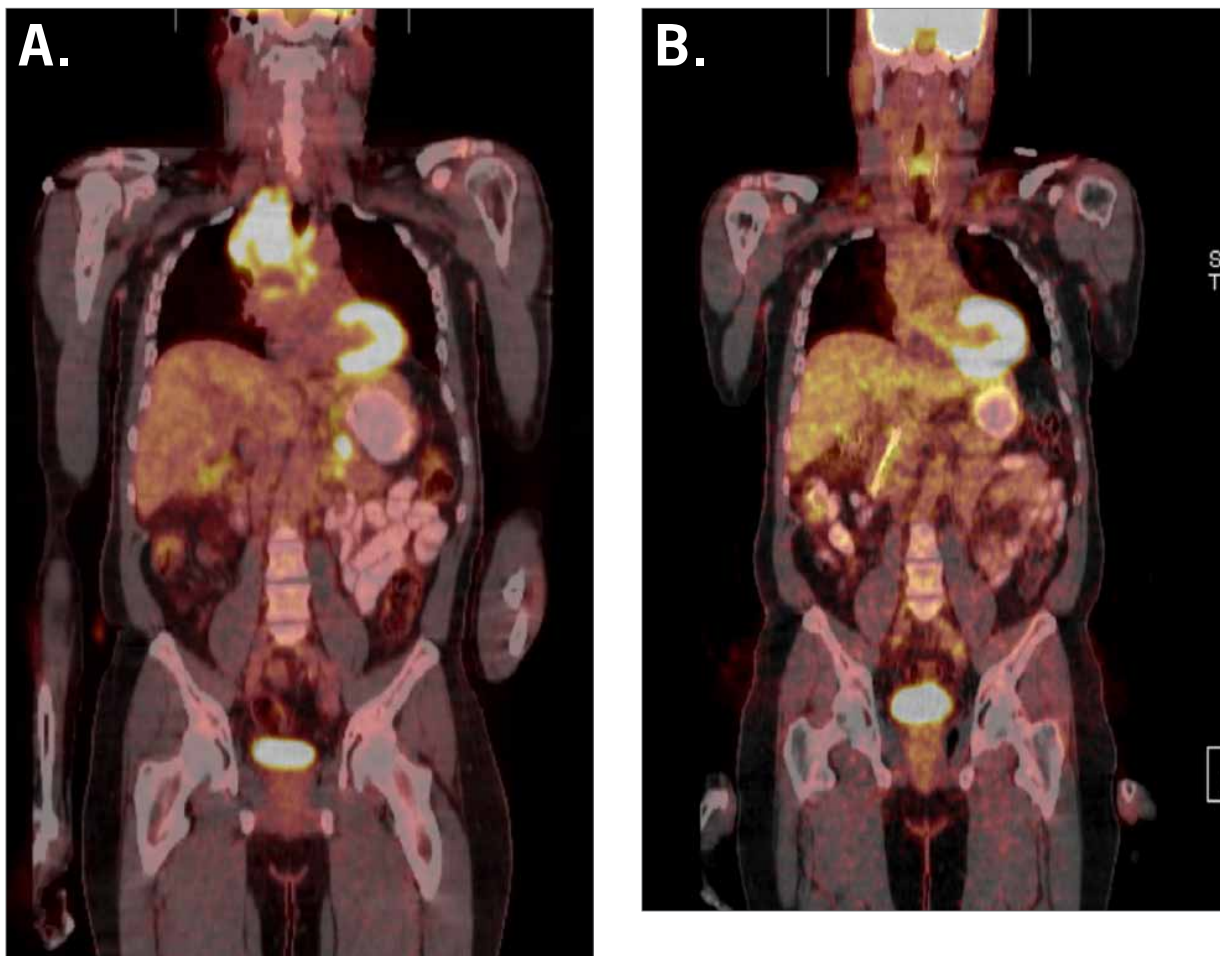
His liver dysfunction improved dramatically following cycle 1, with a decrease in the total bilirubin from 24.3 mg/dL at the time of admission to 11 mg/dL at the time of discharge on day 11. He returned to the hospital on January 27 and underwent endoscopic retrograde cholangiopancreatography (ERCP) with biliary stenting for persistent hyperbilirubinemia; subsequently, his liver function normalized entirely.

Given his excellent response to treatment, the patient was continued on bendamustine plus rituximab administered every 28 days for a total of 6 cycles. He tolerated

the remainder of treatment well, without adverse effects. He exhibited an excellent clinical response (Figure 1). His fatigue and night sweats resolved completely, as did his hoarseness, such that he was able to sing again. PET-CT at 6 months showed no residual disease (Figure 2). It was suggested that he consider autologous stem cell transplant (ASCT), but he declined and continues on watchful waiting. He remains in complete remission almost 1 year following treatment.

## Case 2

Mrs. F. is a 54-year-old woman who presented to her primary care physician with abdominal pain. She was believed to have biliary colic and underwent laparoscopic cholecystectomy. Following surgery, she had continued abdominal pain and diarrhea. Abdominal CT in May 2012 showed no abnormality and it was thought that her symptoms represented irritable bowel syndrome.



**Figure 2.** Fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) for Mr. S. before treatment and following 6 cycles of rituximab and bendamustine. A) Pretreatment PET-CT demonstrating an intensely FDG-avid mediastinal mass (standardized uptake value [SUV]: 22.4), FDG-avid abdominal adenopathy, and intrahepatic FDG uptake. B) PET-CT 6 months post-treatment with 6 cycles of rituximab and bendamustine, with no evidence of residual disease and increased FDG uptake in the area of the previously placed biliary stent.

Continued weight loss and new-onset jaundice prompted a repeat CT in September, which showed diffuse, bulky abdominal adenopathy surrounding the porta hepatis. Her serum bilirubin was 19.5 mg/dL, alkaline phosphatase was 945 mg/dL, and AST and ALT were 201 mg/dL and 167 mg/dL, respectively.

She underwent an ultrasound-guided biopsy that revealed large pleomorphic lymphocytes. Immunohistochemistry stains were positive for CD20, BCL-6, BCL-2, and MUM1, and negative for CD5 and CD10. PET-CT showed bulky fluorodeoxyglucose (FDG)-avid disease in the abdomen, with additional uptake in the liver, bone, and lung. Mrs. S. began treatment with rituximab 375 mg/m<sup>2</sup> and bendamustine 90 mg/m<sup>2</sup> on days 1 and 2. By day 17, her bilirubin was normal, serum AST and ALT were 92 mg/dL and 91 mg/dL, respectively, and alkaline phosphatase had decreased to 321 mg/dL. With the patient's improved liver

function, further treatment was changed to R-CHOP. She is actively undergoing treatment at this time and her liver function has returned to normal.

## Discussion

Treating patients with DLBCL in the setting of hepatic dysfunction is challenging. Cyclophosphamide, doxorubicin, and vincristine all rely on the CYP450 system for metabolism. Elimination through the biliary system is crucial for the excretion of both vincristine and doxorubicin, whereas cyclophosphamide is cleared by the kidney. Accordingly, significant dose reductions of doxorubicin and vincristine would be required.<sup>6</sup> While increased toxicity of cyclophosphamide has not been reported in patients with hepatic dysfunction, most clinicians would recommend dose reductions in the setting of severe liver dysfunction.

Recent data have suggested at least comparable activity with bendamustine plus rituximab when compared to R-CHOP in the upfront treatment of indolent and mantle cell lymphomas.<sup>2,7</sup> Additionally, small series have indicated a response to bendamustine plus rituximab in patients with DLBCL.<sup>3,5,8</sup> Specifically, Weidmann and associates evaluated the upfront use of single-agent bendamustine in 14 patients with a median age of 85 years.<sup>5</sup> A response was observed in 58% of patients, with a complete response rate of 43% and a progression-free survival rate of 7.7 months. The regimen was tolerated with minimal toxicity, even in the setting of advanced age.<sup>2</sup> However, to date, no randomized trials have evaluated the use of bendamustine plus rituximab in the upfront treatment of DLBCL.

The extent to which impaired liver function affects the pharmacokinetics, clinical safety, and effectiveness of bendamustine is not currently known. In vitro studies indicate bendamustine metabolism occurs primarily via CYP1A2-mediated hydrolysis. Conjugation with glutathione within the liver is also likely to play a role.<sup>9,10</sup> The metabolites M3 and M4 are formed, both of which have low cytotoxic activity. While CYP1A2 appears to be an important factor in metabolism, in vitro studies using human liver microsomes show that bendamustine does not significantly inhibit or induce CYP-mediated metabolism.<sup>8,9,11</sup>

Elimination was initially thought to be primarily renal, but recent studies indicate that biliary excretion also plays a role.<sup>8,11</sup> While it appears that important steps in metabolism and possibly excretion of bendamustine and its metabolites occur in the liver, detailed pharmacokinetic studies have shown that mild liver impairment does not affect systemic exposure to bendamustine.<sup>12</sup> Still, caution is advised in treating patients with total bilirubin levels between 1.2 mg/dL and 3.0 mg/dL, with a recommendation against treatment in patients with a bilirubin greater than 3.0 mg/dL.<sup>12,13</sup>

In the cases discussed here, bendamustine was tolerated without adverse effects in patients with a total serum bilirubin more than 10 times the upper limit of normal (ULN). Not only was the treatment tolerable, it also provided a rapid, dramatic, and sustained response. It is important to note that, while both patients had significant burden of intrahepatic and extrahepatic disease, the primary liver impairment was believed to be obstructive in nature and not functional. This impression was supported by the significant elevations in the bilirubin and alkaline phosphatase, out of proportion to AST and ALT. The fact that bendamustine metabolism takes place in the liver, while elimination takes place primarily in the kidney, may explain the observed tolerability.

Similar to our experience, Schoppmeyer and colleagues found bendamustine to be safe and tolerable in a small group of patients with bile duct carcinoma and sig-

nificant hepatic dysfunction.<sup>10</sup> Bendamustine was administered as a 30-minute intravenous infusion at a dose of 140 mg/m<sup>2</sup> on day 1 of the first cycle and at a dose of 100 mg/m<sup>2</sup> on days 1 and 2 of cycles 2–4. Treatment cycles were repeated every 21 days to a maximum of 4 cycles. These 6 patients had baseline AST/ALT and bilirubin levels several times the ULN. The median level of alkaline phosphatase was 10.3 times the ULN and  $\gamma$ -glutamyl transpeptidase levels were 12.2 times the ULN before treatment. All patients experienced significant cytopenias, but no other grade 3/4 nonhematologic toxicities were observed during treatment.<sup>10</sup>

## Conclusion

Bendamustine has demonstrated considerable efficacy in both refractory and previously untreated hematologic malignancies.<sup>2-4,7,8</sup> Furthermore, its application to multiple types of solid tumors has been suggested.<sup>14</sup> Given the increasing evidence of its effectiveness, further understanding of bendamustine's safety and tolerability in special populations, such as those with liver impairment, is crucial. The cases reported here suggest that treating patients with bendamustine, even in the setting of severe hepatic impairment, is safe and effective.

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## Review

### Rituximab Plus Bendamustine for the Treatment of Aggressive Non-Hodgkin Lymphoma Patients With Severe Liver Impairment

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Bendamustine (Treanda, Cephalon), rationally designed to have both alkylating and antimetabolite properties, possesses multiple mechanisms of action, including activation of DNA-damage stress responses and apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe.<sup>1</sup> When combined with rituximab (Rituxan, Genentech/Biogen Idec Pharmaceuticals) in vitro, bendamustine showed synergistic antitumor effects in various leukemia and lymphoma cell lines.<sup>2</sup> Bendamustine alone<sup>3-5</sup> or in combination with rituximab<sup>6,7</sup> demonstrated efficacy and safety in patients with relapsed or refractory, indolent B-cell and mantle cell non-Hodgkin lymphoma (NHL) histologies. The efficacy and safety of bendamustine monotherapy has also been shown in patients with relapsed or refractory aggressive NHL.<sup>8,9</sup> In these clinical trials, all enrolled patients had to have adequate liver function; no patients with severely impaired liver function have been treated in the setting of clinical studies. Thus, no data have been reported in B-cell NHL patients with severe liver impairment treated with bendamustine alone or with rituximab until now.

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McCloskey and associates reported successful treatment results using bendamustine plus rituximab in 2 patients with aggressive B-cell NHL and severe liver impairment.<sup>10</sup> The total serum bilirubin levels in both patients were more than 10 times the upper limit of normal (ULN; 24.3 mg/dL in case 1 and 19.5 mg/dL in case 2), and dramatically improved after treatment, in accordance with excellent responses in both cases. Increased alanine transaminase (ALT) and aspartate transaminase (AST) levels were mild to moderate in each patient, and improved after treatment with bendamustine plus rituximab.

Teichert and colleagues reported that CYP1A2-catalyzed N-dealkylation and gamma hydroxylation are the major routes for bendamustine metabolism, producing 2 metabolites less or similarly toxic to the parent compound.<sup>11</sup> In contrast to the metabolic pathways of the structurally-related chlorambucil, no beta-oxidation of the butanoic acid side chain leading to enhanced toxicity was detected for bendamustine. In a phase II trial of bendamustine plus rituximab in patients with relapsed/refractory aggressive B-cell NHL, no grade 4 AST/ALT elevations were reported. Although grade 3 AST elevations of 3.4% and grade 3 ALT elevations of 8.5% were observed, they were reversible.<sup>9</sup>

The report by McCloskey and coworkers indicates that it may be safe and effective to treat patients with bendamustine, even in the setting of severe hepatic impairment. However, as the authors noted, the severe liver impairment in both cases was not functional, as in hepatitis, but obstructive. Future cautious studies and a better understanding of bendamustine use in patients with severe liver impairment are crucial.

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of today's 2 strategies will be superior in the long term. What we would like to know is the long-term outcomes of today's treatments, but that is not yet possible.

### H&O What are some areas of ongoing research?

**RM** I think that the most immediate priority is to place into context the role of PET scanning and how helpful PET scanning can be in determining treatment options. The second priority is to better understand the biology of Hodgkin lymphoma and the genetic determinants that make up an individual's disease, because not all patients are the same. If we understood the biology at a more personal level for each patient, it may help to better direct therapy. A third avenue includes new types of drugs that are being used to treat Hodgkin lymphoma. These include agents that are antibody-based and use immune strategies to attack the disease. Finally, there are ongoing advances in new types of radiation treatment, where the beams of radiation can become more focused on the areas where the Hodgkin lymphoma exists and attempt to achieve benefits while reducing radiation to the surrounding tissues.

### H&O What are the biggest remaining challenges?

**RM** I think one of the biggest challenges is the conundrum I have described, where what is really important

for these patients is their long-term outcomes. There will always be this issue of wanting to understand the long-term outcomes associated with today's treatments. By the time we understand the long-term outcomes of today's treatments, a decade or more will have passed and there will be advances, which will result in another generation of questions. Thus, we will constantly have this tension of trying to take what we have learned from understanding the long-term outcomes and place it into the context of modern treatment. I think the other challenge that exists is that although Hodgkin lymphoma has exemplified a success in treating patients with cancer, we lack true understanding of how to target treatment against the very specific genetic determinants of the disease. If we could have a better understanding of that biology, there may be more opportunities for better treatment.

### Suggested Readings

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