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Bendamustine

Updated: September 1, 2017.

OVERVIEW

Introduction

Bendamustine is a parenterally administered alkylating agent used alone and in combination with other antineoplastic agents in the treatment of chronic lymphocytic leukemia and refractory forms of non-Hodgkin lymphoma. Bendamustine therapy is associated with minor transient serum enzyme elevations during treatment and to rare instances of clinically apparent liver injury, with jaundice generally arising as a part of a generalized hypersensitivity syndrome. Bendamustine also has potent immunosuppressive activity and can cause reactivation of chronic hepatitis B that can be severe and even fatal.

Background

Bendamustine (ben" da mus' teen) is a relatively novel alkylating agent with a benzimidazole ring giving it purine analogue-like properties. Like other alkylating agents, bendamustine is thought to act by modifying and cross linking purine bases in DNA, thus inhibiting DNA, RNA and protein synthesis and leading to cell death in rapidly dividing cells. Bendamustine appears to have a special activity against B cell leukemias and lymphomas. Bendamustine was approved for use in the United States in 2008 as therapy for chronic lymphocytic leukemia, and indications were later expanded to include indolent B cell non-Hodgkin lymphoma that is refractory to rituximab containing regimens. Bendamustine is given intravenously and is available in liquid formulations (45 and 180 mg vials: 90 mg/mL) and as powder for reconstitution (25 or 100 mg in a single use vial) generically and under the trade name Treanda. Recommended doses vary by age, body weight and malignant condition. Bendamustine is often given in combination with other antineoplastic agents on days 1 and 2 of 21- or 28-day cycles. The toxicity of bendamustine is similar to that of other alkylating agents. Common side effects include bone marrow suppression, nausea, vomiting, diarrhea, anorexia, fatigue, dizziness and hypersensitivity rashes. Serious adverse events include severe myelosuppression, bacterial infections, infusion reactions, local extravasation injury, anaphylaxis, tumor lysis syndrome and Stevens Johnson syndrome.

Hepatotoxicity

Mild and transient elevations in serum aminotransferase levels are found in up to 20% of patients treated with bendamustine, but elevations above 5 times the upper limit of normal occur in less than 3% of patients. The abnormalities are generally transient, unaccompanied by symptoms and rarely require dose modification. Clinically apparent liver injury from bendamustine has been limited to a small number of cases of mild hepatitis with features of hypersensitivity including eosinophilia, rash or other systemic symptoms. Autoantibody formation is uncommon. The course is generally self-limited, but may require corticosteroid therapy for control of symptoms and timely recovery.

Bendamustine therapy has also been implicated in causing reactivation of hepatitis B in patients with anti-HBc in serum with or without HBsAg. In several instances patients were also receiving corticosteroids or rituximab, yet had received these without reactivation in the past. Reactivation arose after 2 to 6 cycles of bendamustine chemotherapy, presenting with symptoms accompanied by HBsAg and rising levels of HBV DNA in serum. Reactivation was generally self-limited and patients later became HBsAg negative. In one instance, however, the course was severe and resulted in death from acute liver failure.

Likelihood score: C (probable cause of clinically apparent liver injury, some of which is due to reactivation of hepatitis B).

Mechanism of Injury

The mild serum aminotransferase elevations that occur with bendamustine therapy are most likely due to direct hepatotoxicity and are generally mild, asymptomatic and resolve without dose modification or intervention. The more clinically apparent forms of bendamustine hepatotoxicity are likely due to hypersensitivity. Bendamustine is rarely used in myeloablative regimens in preparation of hematopoietic cell transplantation and has not been linked to cases of sinusoidal obstruction syndrome, although in high enough doses it is likely to cause sinusoidal cell injury as do other alkylating agents. Bendamustine also appears to be capable of causing reactivation of hepatitis B, probably because of its potent immunosuppressive activity. Bendamustine is extensively metabolized by the hepatic cytochrome P450 system, predominantly CYP 1A2, and may be susceptible to drug-drug interactions with agents that induce or inhibit CYP 1A2 activity.

Outcome and Management

The severity of liver injury from bendamustine ranges from mild elevations in liver enzymes to anicteric, but symptomatic hepatitis to clinically apparent hepatitis with jaundice. Monitoring of liver tests during therapy is recommended. Cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome have not been reported. Patients with hypersensitivity reactions to bendamustine should not be reexposed to the agent. There is no information on the cross reactivity of hypersensitivity reactions to bendamustine with other alkylating agents such as mechlorethamine (nitrogen mustard), carmustine (CCNU), lomustine (BCNU), chlorambucil and cyclophosphamde. Because bendamustine can cause reactivation of hepatitis B, patients should be screened for HBsAg and anti-HBc before starting therapy and either offered prophylaxis with agents active against hepatitis B (entecavir, tenofovir) or monitored closely for HBV DNA levels and started on therapy if viral titers rise.

Drug Class: Antineoplastic Agents, Alkylating Agents

CASE REPORT

Case 1. Acute hypersensitivity reaction with hepatitis attributed to bendamustine

[Modified from: Jo T, Horio K. Severe liver damage and nonallergic bronchitis with eosinophilia in a patient with follicular lymphoma treated with bendamustine plus rituximab. Case Rep Oncol 2014; 7: 497-502. PubMed Citation].

A 66 year old woman with follicular lymphoma developed cough and liver test abnormalities 16 days after starting an initial cycle of bendamustine and rituximab. She had the recent diagnosis of stage IIIa follicular lymphoma with multiple lymph node involvement. After a first course of R-CHOP therapy, she refused further courses because of peripheral neuropathy, alopecia and fatigue. For these reasons, she was switched to rituximab (375 mg/m^2 on day 1) and bendamustine (75 mg/m^2 on days 2 and 3 of planned 21 day cycles). She developed a severe cough that caused insomnia and fatigue and was found to have bronchitis and liver test abnormalities

with ALT 93 U/L, AST 133 U/L, alkaline phosphatase 274 U/L and bilirubin 0.7 mg/dL. She had no history of smoking, drug allergies or know exposure to hepatitis. Tests for acute hepatitis A, B and C were negative as were assays for CMV and mycoplasma infection. Imaging of the liver was normal and a CT scan of the chest showed no evidence of pneumonitis. Her cough continued, but cultures were negative and she was evidently afebrile. At the same time liver tests worsened; serum bilirubin rising to 6.2 mg/dL, ALT to 577 U/L and alkaline phosphatase to 932 U/L (Table). Peripheral eosinophil counts, that had been normal initially, began to rise (peaking at 36%). Because of worsening symptoms and laboratory test results suggesting a hypersensitivity reaction, she was treated with a short course of high dose methylprednisolone and improved rapidly. She was switched to oral prednisone which was gradually reduced in dose and then discontinued. In follow up, her cough resolved and liver tests were normal. Bendamustine was not restarted.

Key Points

Medication:	Bendamustine (2 doses of 75 mg/m^2 intravenously)
Pattern:	Mixed (R=~4.5)
Severity:	3+ (jaundice, hospitalized)
Latency:	2 weeks
Recovery:	Within 2 months (incomplete)
Other medications:	Rituximab, no other mediations mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Eosinophils (%)	Bilirubin (mg/dL)	Other
Pre (-2 days)	0	12	285	3%	0.6	
Day 1	0					iv rituximab
Day 2-3	0					iv bendamustine
9 days	7 days	12	268	7%	2.9	
16 days	14 days	93	274	1%	0.7	Cough and fatigue
28 days	26 days	477	947	2%	1.4	Admission
31 days	29 days	557	932	18%	3.1	GGT 422 U/L
34 days	32 days	577	900	19%	5.6	
41 days	39 days	466	731	36%	6.2	
44 days	42 days	365	693	34%	4.5	Methylprednisolone
50 days	7 weeks	73	409	5%	2.2	Prednisone
58 days	8 weeks	23	266	2%	1.1	Prednisone
64 days	9 weeks	16	250	1%	1.2	
90 days	3 months	13	242	0%	1.0	
Normal Values (est.)		**<40**	**<280**	**<5%**	**<1.2**	

Comment

A woman with follicular lymphoma developed a hypersensitivity reaction within 2 weeks of starting an initial cycle of rituximab and bendamustine. The major symptoms were cough and fatigue which appeared to be due to an allergic bronchitis. Accompanying this was a mild hepatitis that nevertheless progressed to jaundice and was accompanied by a rising eosinophilia. Treatment with corticosteroids rapidly brought the hypersensitivity

reaction under control and her liver tests were normal within 4 to 6 weeks and remained normal even with tapering and discontinuation of corticosteroids. There was evidently no rash or fever, so that the reaction is best described as "drug-hypersensitivity with systemic symptoms" rather than DRESS syndrome. One might hypothesize that rituximab altered the clinical expression of the hypersensitivity reaction. Hypersensitivity reactions (usually rash) are not infrequent with bendamustine therapy (1% to 4%) but are generally mild and self-limited, although rare instances of Stevens Johnson syndrome have been reported.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Bendamustine – Treanda®

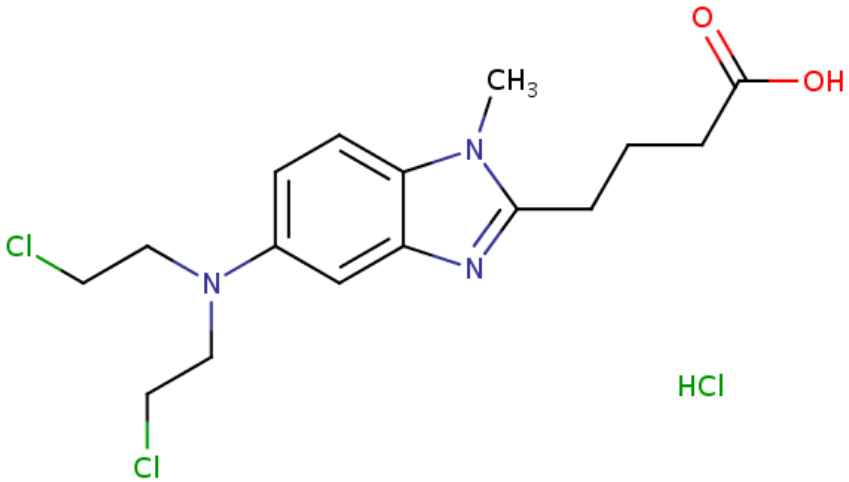
DRUG CLASS

Antineoplastic Agents, Alkylating Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Bendamustine	3543-75-7	C16-H21-Cl2-N3-O2.Cl-H	

ANNOTATED BIBLIOGRAPHY

References updated: 01 September 2017

Zimmerman HJ. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of cancer chemotherapeutic agents published in 1999, before the availability of bendamustine).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 541-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents; no mention of bendamustine).

Chabner BA, Bertino J, Clearly J, Ortiz T, Lane A, Supko JG, Ryan DP. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1677-730.

(Textbook of pharmacology and therapeutics).

Friedberg JW, Cohen P, Chen L, Robinson KS, Forero-Torres A, La Casce AS, Fayad LE, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008; 26: 204-10. PubMed PMID: 18182663.

(Among 76 patients with refractory non-Hodgkin lymphoma treated with bendamustine monotherapy [days 1 and 2 in 21 day cycles], the overall response rate was 77% and adverse events were common, but ALT elevations and hepatotoxicity were not mentioned).

Knauf WU, Lissichkov T, Aldaoud A, Liberati A, Loscertales J, Herbrecht R, Juliusson G, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009; 27: 4378-84. PubMed PMID: 19652068.

(Among 319 patients with chronic lymphocytic leukemia treated with bendamustine [iv on days 1 and 2] or chlorambucil [orally] in 28 day cycles for up to 6 months, the complete response rate was higher with bendamustine [31% vs 2%], but side effects were also more common; no mention of ALT elevations or hepatotoxicity).

Kahl BS, Bartlett NL, Leonard JP, Chen L, Ganjoo K, Williams ME, Czuczman MS, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer 2010; 116: 106-14. PubMed PMID: 19890959.

(Among 100 patients with refractory B cell lymphoma treated with bendamustine [iv on days 1 and 2 in 6 to 8 21-day cycles], the overall response rate was 75% and side effects were common and included 39 serious adverse events and 7 deaths, but none were attributed to liver injury).

Alamdari HS, Pinter-Brown L, Cassarino DS, Chiu MW. Severe cutaneous interface drug eruption associated with bendamustine. Dermatol Online J 2010; 16: 1. PubMed PMID: 20673529.

(75 year old man with B cell lymphoma developed diffuse erythematous desquamating rash 5 days after a second course of bendamustine which responded slowly to prednisone therapy; no mention of liver test abnormalities).

Cheson BD, Friedberg JW, Kahl BS, Van der Jagt RH, Tremmel L. Bendamustine produces durable responses with an acceptable safety profile in patients with rituximab-refractory indolent non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2010; 10: 452-7. PubMed PMID: 21189660.

(Among 161 patients with rituximab-refractory indolent non-Hodgkin lymphoma treated with bendamustine in two open labelled trials [Kahl 2010 & Freiberg 2008], the overall and complete response rates were 76% and 23%, but side effects were common including hematologic [~94%], febrile neutropenia [11%], nausea [75%], infection [61%], fatigue [57%], diarrhea [39%], anorexia [23%] and secondary malignancies [5%]; no mention of ALT elevations or hepatotoxicity).

Tapan U, May SK, Fiore J, Kozyreva O. Reactivation of hepatitis B virus following bendamustine-containing chemotherapy in a patient with multiple myeloma. Leuk Lymphoma 2011; 52: 916-8. PubMed PMID: 21306291.

(64 year old man with myeloma developed reactivation of hepatitis B after two cycles of bendamustine and dexamethasone [bilirubin 10.1 mg/dL, ALT 1759 U/L, Alk P 85 U/L, INR 1.6, HBV DNA 8.7 million IU/mL, HBsAg positive], dying one month later despite entecavir therapy and HBV DNA decline to 400 IU/mL]).

Lock G, Helmich F, Bertram M. [Impending liver failure after chemoimmunotherapy-induced reactivation of hepatitis B - successful treatment with entecavir]. Dtsch Med Wochenschr 2012; 137: 1248-50. PubMed PMID: 22644491.

(83 year old woman with leukemia developed acute reactivation of hepatitis B after 6 cycles of bendamustine and rituximab [bilirubin 27.8 mg/dL, ALT 1353 U/L, INR 1.7, HBV DNA 1.6 million IU/mL, HBsAg positive], resolving with entecavir therapy and later becoming HBsAg negative and anti-HBs positive).

Tsutsumi Y, Ogasawara R, Miyashita N, Tanaka J, Asaka M, Imamura M. HBV reactivation in malignant lymphoma patients treated with rituximab and bendamustine. Int J Hematol 2012; 95: 588-91. PubMed PMID: 22419099.

(79 and 53 year old women, with multiple previous courses of rituximab and CHOP and anti-HBc without HBsAg in serum, developed reactivation of hepatitis B after 2 and 4 courses of bendamustine and rituximab [mild symptoms, bilirubin not given, ALT 340 and 68 U/L, HBV DNA 3.7 and 8.8 log copies/mL and HBsAg in serum], both resolving with entecavir therapy).

Rago A, Ridola L, Lichtner M, Mecarocci S, Marocco R, Cenfra N, Belvisi V, et al. Hepatitis B reactivation despite entecavir prophylaxis in a patient with chronic lymphocytic leukaemia receiving bendamustine. J Antimicrob Chemother 2012; 67: 510-1. PubMed PMID: 22110085.

(Patient with CLL and HBsAg in serum [HBV DNA negative] was started on bendamustine and given prophylactic entecavir but nevertheless developed rising levels of HBV DNA [1.3 million IU/mL] and mild enzyme elevations [ALT 73 U/L], which responded to adding tenofovir and using higher doses of entecavir; patient later tolerated chemotherapy without further evidence of reactivation).

Fischer K, Cramer P, Busch R, Böttcher S, Bahlo J, Schubert J, Pflüger KH, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012; 30: 3209-16. PubMed PMID: 22869884.

(Among 117 patients with previously untreated chronic lymphocytic leukemia treated with bendamustine and rituximab in 21 day courses, response rates were 88% overall of which 23% were complete, and side effects included severe hematologic adverse events in 27%, infections in 8% and allergic reactions in 9%; no mention of ALT elevations or hepatotoxicity).

Ohmachi K, Niitsu N, Uchida T, Kim SJ, Ando K, Takahashi N, Takahashi N, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013; 31: 2103-9. PubMed PMID: 23650408.

(Among 59 patients with refractory B cell lymphoma treated with bendamustine [days 2 and 3] and rituximab [day 1] in 21 day cycles, the overall response rate was 63% and side effects were common, both hematologic and nonhematologic; no mention of ALT elevations or hepatotoxicity).

Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, Kofahl-Krause D, et al.; Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013; 381 (9873): 1203-10. PubMed PMID: 23433739.

(Among 549 patients with previously untreated indolent mantel cell lymphomas treated with rituximab and either bendamustine or CHOP, bendamustine had lower rates of severe hematologic toxicity, alopecia, stomatitis, infections and neuropathies but more cases of rash; no mention of ALT elevations or hepatotoxicity).

Jo T, Horio K. Severe liver damage and nonallergic bronchitis with eosinophilia in a patient with follicular lymphoma treated with bendamustine plus rituximab. Case Rep Oncol 2014; 7: 497-502. PubMed PMID: 25232317.

(66 year old woman with follicular lymphoma developed liver test abnormalities 16 days after receiving a first cycle of bendamustine and rituximab [bilirubin rising from 0.7 to 6.2 mg/dL, ALT 133 to 557 U/L, Alk P 274 to 947 U/L], with eosinophilia and bronchitis, resolving within 3 weeks on prednisone therapy: Case 1).

Flinn IW, van der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D, Hertzberg M, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014; 123: 2944-52. PubMed PMID: 24591201.

(Among 447 patients with indolent non-Hodgkin or mantle cell leukemia treated with up to 6 cycles of either bendamustine with rituximab or standard therapy [R-CHOP or R-CVP], overall response rates were 97% vs 91% and complete response 31% vs 25%; side effects of nausea, vomiting and hypersensitivity were more common with bendamustine and alopecia and neuropathies less frequent; most common reasons for discontinuing bendamustine were neutropenia, thrombocytopenia and rash; no mention of ALT elevations or hepatotoxicity).

Cortelezzi A, Sciumè M, Liberati AM, Vincenti D, Cuneo A, Reda G, Laurenti L, et al. Bendamustine in combination with ofatumumab in relapsed or refractory chronic lymphocytic leukemia: a GIMEMA Multicenter Phase II Trial. Leukemia 2014; 28: 642-8. PubMed PMID: 24220274.

(Among 47 patients with refractory chronic lymphocytic leukemia treated with up to six 28-day cycles of bendamustine and ofatumumab, response rates were 72% overall of which 17% were complete, and severe adverse events were largely hematologic, with severe infections in 6%, tumor lysis syndrome in 4%, but no ALT or AST elevations above 5 times ULN).

Czuczman MS, Goy A, Lamonica D, Graf DA, Munteanu MC, van der Jagt RH. Phase II study of bendamustine combined with rituximab in relapsed/refractory mantle cell lymphoma: efficacy, tolerability, and safety findings. Ann Hematol 2015; 94: 2025-32. PubMed PMID: 26411584.

(Among 45 patients with refractory mantle cell lymphoma treated with bendamustine and rituximab in 28 day cycles, response rates were 82% overall [40% complete] and adverse events included nausea [69%], fatigue [57%], anorexia [42%], severe infections [16%], but there were no liver related severe adverse events, discontinuations or deaths).

Kouroukis CT, Crump M, MacDonald D, Larouche JF, Stewart DA, Johnston J, Sauvageau S, et al. An open-label expanded-access trial of bendamustine in patients with rituximab-refractory indolent non-Hodgkin lymphoma or previously untreated chronic lymphocytic leukemia: BEND-ACT. Curr Oncol 2015; 22: 260-71. PubMed PMID: 26300664.

(Among 90 patients with rituximab refractory chronic lymphocytic leukemia or non-Hodgkin lymphoma treated with bendamustine in 21 or 28 day cycles, side effects included nausea [70%], fatigue [57%], diarrhea [33%], myelosuppression, febrile neutropenia [6%] and tumor lysis syndrome [2%], but there no liver related severe adverse events, discontinuations or deaths).

Luminari S, Goldaniga M, Cesaretti M, Orsucci L, Tucci A, Pulsoni A, Salvi F, et al. A phase II study of bendamustine in combination with rituximab as initial treatment for patients with indolent non-follicular non-Hodgkin lymphoma. Leuk Lymphoma 2016; 57: 880-7. PubMed PMID: 26379040.

(Among 65 patients with advanced, indolent non-Hodgkin lymphoma treated with bendamustine and rituximab in 28 day cycles, the response rate was 86% overall [complete in 48%] and serious adverse events were largely hematologic and 3% developed febrile neutropenia; no mention of ALT elevations or hepatotoxicity).

Gentile M, Zirlik K, Ciolli S, Mauro FR, Di Renzo N, Mastrullo L, Angrilli F, et al. Combination of bendamustine and rituximab as front-line therapy for patients with chronic lymphocytic leukaemia: multicenter, retrospective clinical practice experience with 279 cases outside of controlled clinical trials. Eur J Cancer 2016; 60: 154-65. PubMed PMID: 27127905.

(Retrospective analysis of 279 patients with chronic lymphocytic leukemia treated with 1 to 6 28-day cycles of bendamustine and rituximab found an overall response rate of 86% [25% complete] and severe adverse event rate of 41%, neutropenia 28%, infections 8.6% and rash 5.1%; among 10 patients who died one died of fulminant hepatitis, but no details given).

Rummel M, Kaiser U, Balser C, Stauch M, Brugger W, Welslau M, Niederle N, et al.; Study Group Indolent Lymphomas. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol 2016; 17: 57-66. PubMed PMID: 26655425.

(Among 219 patients with relapsed indolent or mantle cell lymphomas treated with rituximab and either bendamustine or fludarabine in up to 6 28-day cycles, overall response rates were higher with bendamustine [82% vs 54%] as were complete responses [40% vs 18%], while side effect rates were similar; ALT or AST elevations occurred in 19% vs 9%, but were less than 3 times ULN in all; one patient receiving rituximab and fludarabine developed "toxic hepatitis", but no details given).

Flinn IW, Panayiotidis P, Afanasyev B, Janssens A, Grosicki S, Homenda W, Smolej L, et al. A phase 2, multicenter study investigating ofatumumab and bendamustine combination in patients with untreated or relapsed CLL. Am J Hematol 2016; 91: 900-6. PubMed PMID: 27222473.

(Among 44 patients with previously untreated and 53 with refractory chronic lymphocytic leukemia treated with bendamustine and ofatumumab in 2 to 6 28-day cycles, the overall response rate was 95% and 74% [complete in 43% and 11%] and "no unexpected toxicities were reported").