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Tositumomab

Updated: June 12, 2015.

OVERVIEW

Introduction

Tositumomab is the combination of a monoclonal antibody to CD20 and iodine-131 which is used to treat refractory, advanced non-Hodgkin lymphoma. Tositumomab has not been associated with significant serum enzyme elevations during therapy or to cases of idiosyncratic, clinically apparent liver injury. However, tositumomab has potent immunosuppressive activity and is probably capable of causing reactivation of hepatitis B in susceptible patients.

Background

Tositumomab (toe si tue' moe mab) is a monoclonal antibody to the cell surface antigen CD20 (also known as human B lymphocyte restricted differentiation antigen: Bp35) which is found on mature B cells as well as 90% of neoplastic B cell such as occur in non-Hodgkin lymphoma. Engagement of tositumomab with CD20 leads to cell lysis and depletion of circulating and tissue B cells for 6 to 8 months. Tositumomab is given in combination with iodine-131 radiolabelled tositumomab which provides additional antineoplastic activity. Tositumomab and tositumomab I-131 were approved for use in previously treated, resistant non-Hodgkin lymphoma in the United States in 2003. Because of declining use and the availability of other anti-CD20 monoclonal antibodies, however, tositumomab was discontinued by its sponsor in 2014. Tositumomab was previously available in liquid solution in single use vials of 35 and 225 mg (14 mg/mL) and as Iodine 131 tositumomab solutions of varying concentrations. Dosing required a 2 part dosimetric step followed 7 to 14 days later by a 2-part therapeutic step. Tositumomab was meant to be given only for a single course. Common side effects included infusion reactions, chills, fever, nausea, fatigue, anemia, thrombocytopenia, neutropenia and infections. Less common but potentially severe side effects included severe allergic reactions, anaphylaxis, marked bone marrow suppression, thyroid abnormalities and radiation exposure.

Hepatotoxicity

Serum aminotransferase elevations are uncommon during tositumomab therapy and rarely mentioned in large clinical trials of its use in non-Hodgkin lymphoma. Clinically apparent liver injury has not been reported with tositumomab therapy either in prelicensure clinical trials or subsequent to its more widescale clinical use.

On the other hand, other monoclonal antibodies to CD20 such as rituximab and ofatumumab are well known to cause reactivation of hepatitis B. Specific features of the reactivation caused by tositumomab have not been published, but HBV reactivation is typically associated with acute hepatocellular injury that can be severe and lead to acute liver failure and death or need for emergency liver transplantation. Reactivation typically occurs in patients who are HBsAg carriers with inactive hepatitis B who undergo chemotherapy for cancer. Reactivation

can also occur in persons who have recovered from hepatitis B, who have no detectable HBsAg, but have antibody to hepatitis B core antigen (anti-HBc) with or without antibody to HBsAg (anti-HBs) in serum. The usual sequence of events is appearance of rising levels of HBV DNA in serum shortly after chemotherapy is started followed by rise in levels of HBsAg and HBeAg. When therapy is stopped and immune reconstitution has begun, serum ALT and AST levels rise, which is followed by symptoms and jaundice. The onset of liver injury is delayed and may occur months after 3 to 6 courses of therapy. Reactivation of hepatitis B tends to be severe and the mortality rate in jaundiced cases exceeds 10%. Liver histology demonstrates an acute hepatitis like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. Restarting chemotherapy can result in recurrence of injury, although concurrent antiviral treatment may block recurrence. Many cases of hepatitis B reactivation have been reported with rituximab therapy; the occurrence with tositumomab has been implied but specific cases have not been published.

Mechanism of Injury

The mechanism of liver injury in reactivation of hepatitis B appears to be a brisk immunological response to newly expressed viral antigens on hepatocytes. Injury generally arises after immunosuppressive or cancer chemotherapy has stopped or between courses of treatment.

Outcome and Management

Guidelines for management of patients who are to receive tositumomab recommend routine screening for hepatitis B before starting treatment. Screening should include tests for HBsAg and anti-HBc (and perhaps also anti-HBs as this may help in management). Prophylaxis with a potent oral, antiviral agent effective against hepatitis B is recommended for all persons who have HBsAg in serum and is suggested for those with anti-HBc without HBsAg. An alternative approach is careful monitoring for HBV DNA during therapy and early institution of antiviral therapy if levels rise.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tositumomab – Bexxar®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Tositumomab	208921-02-2	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 June 2015

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; no specific discussion of tositumomab).

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Vose JM, Wahl RL, Saleh M, Rohatiner AZ, Knox SJ, Radford JA, Zelenetz AD, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000; 18: 1316-23. PubMed PMID: 10715303.

(Among 47 patients with chemotherapy relapsed non-Hodgkin lymphoma treated with iodine-131 labelled tositumomab, clinical responses occurred in 57% and side effects included fatigue [41%], nausea [38%], fever [34%], infections, rash and fatigue; no mention of ALT elevations or hepatotoxicity).

Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L, Lister TA, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001; 19: 3918-28. PubMed PMID: 11579112.

(Among 60 patients with previously treated non-Hodgkin lymphoma treated with iodine-I 131 labelled tositumomab, 65% had a partial or complete response; adverse events included fatigue, fever, nausea, pruritus, poor appetite and hypotension; no mention of ALT elevations or hepatotoxicity).

Rutar FJ, Augustine SC, Kaminski MS, Wahl RL, Siegel JA, Colcher D. Feasibility and safety of outpatient Bexxar therapy(tositumomab and iodine I 131 tositumomab) for non-Hodgkin's lymphoma based on radiation doses to family members. Clin Lymphoma 2001; 2: 164-72. PubMed PMID: 11779293.

(Analysis of radiation doses of family members of recipients of iodine I-131 labelled tositumomab).

Iodine-131 tositumomab (Bexxar) for treatment of lymphoma. Med Lett Drugs Ther 2003; 45 (1168): 86-7. PubMed PMID: 14576623.

(Concise review of the efficacy, safety and costs of tositumomab shortly after its approval in the US; most patients develop neutropenia, thrombocytopenia and anemia and half have an infectious complications, 8% requiring hospitalization; no mention of hepatotoxicity or ALT elevations).

Davies AJ, Rohatiner AZ, Howell S, Britton KE, Owens SE, Micallef IN, Deakin DP, et al. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2004; 22: 1469-79. PubMed PMID: 15084620.

(Among 41 patients with non-Hodgkin lymphoma treated with tositumomab, response rates were 76% and toxicity was principally hematologic; no mention of ALT elevations or hepatotoxicity).

Kaminski MS, Radford JA, Gregory SA, Leonard JP, Knox SJ, Kroll S, Wahl RL. Re-treatment with I-131 tositumomab in patients with non-Hodgkin's lymphoma who had previously responded to I-131 tositumomab. J Clin Oncol 2005; 23: 7985-93. PubMed PMID: 16204016.

(Among 32 patients with advanced non-Hodgkin lymphoma who were retreated with tositumomab, 18 had a complete or partial response and adverse events were similar to those during the initial therapy although 5 patients developed a myelodysplastic syndrome 8-62 months after initial therapy; no mention of ALT elevations or hepatotoxicity).

Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, Regan D, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005; 352: 441-9. PubMed PMID: 15689582.

(Among 76 patients with advanced follicular B-cell lymphoma treated with tositumomab, 75% had a complete response and toxicity was common, but usually mild-to-moderate, hematologic adverse events being most common; no mention of ALT elevations or hepatotoxicity).

Witzig TE, Fishkin P, Gordon LI, Gregory SA, Jacobs S, Macklis R, McLaughlin P, et al. Treatment recommendations for radioimmunotherapy in follicular lymphoma: a consensus conference report. Leuk Lymphoma 2011; 52: 1188-99. PubMed PMID: 21599576.

(Consensus statement on use of radioimmunotherapy for follicular lymphoma; no mention of hepatotoxicity).

Press OW, Unger JM, Rimsza LM, Friedberg JW, LeBlanc M, Czuczman MS, Kaminski M, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131) iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol 2013; 31: 314-20.

(Among 496 patients with previously untreated non-Hodgkin lymphoma who were treated with CHOP and either rituximab or I-131 tositumomab, objective responses [94% vs 84%] and both progression free and overall survival [92% vs 86% at 5 years] were similar in the two groups, as were adverse events including secondary malignancies [8% vs 9%]; no mention of ALT elevations or hepatotoxicity).

Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. JAMA 2013; 310: 1664. PubMed PMID: 24150447.

(News report of the FDA alert to physicians of the high risk of HBV reactivation in patients receiving ofatumumab or rituximab, two monoclonal antibodies to CD20).