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Tositumomab

Updated: April 15, 2020.

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 radiolabeled 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 general 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.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury and possibly reactivation of hepatitis B).

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: 15 April 2020

Abbreviations: TNF, tumor necrosis factor.

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 tumor necrosis factor [TNF] alpha antagonists"; no specific discussion of tositumomab).

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway-targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1203-36.

(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. PubMed PMID: 23233710.

(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).

Goldsmith SJ. Targeted radionuclide therapy: A historical and personal review. Semin Nucl Med. 2020;50:87–97. PubMed PMID: 31843064.

(Review of the history of development of radionuclide therapy using monoclonal antibodies to target the radioactivity including tositumomab, which was withdrawn by its sponsor for economic rather than scientific or safety issues).

Sachpekidis C, Jackson DB, Soldatos TG. Radioimmunotherapy in non-Hodgkin's lymphoma: retrospective adverse event profiling of Zevalin and Bexxar. Pharmaceuticals (Basel). 2019;12:E141. pii. PubMed PMID: 31546999.

(Review of adverse event reports made to the FDA and WHO for tositumomab demonstrated an increase after 2003 to a peak in 2005 and subsequent gradual decrease, correlating with change in usage; most common adverse events were myelodysplastic syndrome, fever, acute myeloid leukemia, fatigue and nausea; liver injury and ALT elevations were not mentioned).

Shadman M, Li H, Rimsza L, Leonard JP, Kaminski MS, Braziel RM, Spier CM, et al. Continued excellent outcomes in previously untreated patients with follicular lymphoma after treatment with CHOP plus

rituximab or CHOP plus (131)I-tositumomab: long-term follow-up of phase III randomized study SWOG-S0016. J Clin Oncol. 2018;36:697–703. PubMed PMID: 29356608.

(Long term follow up of trial comparing R-CHOP to CHOP with tositumomab [Press 2013] found radiotherapy resulted in better progression-free survival but similar overall survival, the occurrence of deaths from leukemia and myelodysplastic syndrome with radiation exposure being greater; no mention of hepatotoxicity or liver related deaths).

Hadid T, Raufi A, Kafri Z, Mandziara M, Kalabat J, Szpunar S, Kolizeras K, et al. Safety and efficacy of radioimmunotherapy (RIT) in treatment of non-Hodgkin's lymphoma in the community setting. Nucl Med Biol. 2016;43:227–31. PubMed PMID: 27067042.

(Among 48 patients with refractory or relapsed malignant non-Hodgkin lymphoma treated at a community center with tositumomab, overall median survival was 48 months and the major toxicities were hematologic; no mention of ALT elevations or hepatotoxicity).

Leonard JP, Gregory SA, Smith H, Horner TJ, Williams VC, Giampietro P, Lin TS. CHOP chemotherapy followed by tositumomab and Iodine-131 tositumomab for previously untreated diffuse large B-cell lymphoma. Clin Lymphoma Myeloma Leuk. 2016;16:191–6. PubMed PMID: 26832194.

(Among 15 patients with non-Hodgkin lymphoma treated with tositumomab after completing 6 cycles of CHOP, the response rate increased from 60% to 80% and adverse events included bone marrow suppression as well as fatigue [72%], dyspnea, headache and pain; no mention of ALT elevations or hepatotoxicity).