U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Blinatumomab. [Updated 2017 Sep 30].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Blinatumomab

Updated: September 30, 2017.

OVERVIEW

Introduction

Blinatumomab is a recombinant mouse derived bispecific monoclonal antibody to the CD3 cell surface antigen found on T lymphocytes and the CD19 site for the targeted (malignant) B lymphocytes. Blinatumomab is approved for use as a second line treatment of relapsed or refractory B cell precursor related acute lymphoblastic leukemia (ALL). Blinatumomabis commonly associated with mild-to-moderate serum enzyme and bilirubin elevations during the first cycle of therapy, but it has not been linked to cases of clinically apparent liver injury.

Background

Blinatumomab (blin" a toom' oh mab) is a mouse monoclonal IgG1 antibody that has bispecific reactivity to both the CD3 cell surface antigen that is found on normal T cells and the CD19 antigen that is overexpressed on B cell malignancies. The monoclonal antibody binds to T cells and brings them into contact with malignant B cells, allowing them to recognize and eliminate ALL blasts. Blinatumomab has been evaluated in children and adults with relapsed or refractory acute lymphoblastic leukemia (ALL) and shown to induce a high rate of clinical response and to prolong overall survival in comparison to conventional chemotherapy. Blinatumomab was approved for use in patients with Philadelphia chromosome-negative, relapsed or refractory, B cell precursor-related ALL in 2014. Blinatumomab is available as a powder for reconstitution in single use vials of 35 µg under the brand name Blincyto. Blinatumomab is given by constant intravenous infusion in variable daily doses [9 or 28 µg in persons 45 kg or greater] for 28 days per cycle. Side effects are common and can be severe, including infusion reactions, chills, fever, nausea, diarrhea, fatigue, dyspnea, cough, bronchitis, pneumonia, skin rash, neutropenia and infections. Less common, but potentially severe side effects include cutaneous reactions (Stevens Johnson syndrome), tumor lysis syndrome, pancreatitis, neurological toxicities, prolonged neutropenia, thrombocytopenia and anemia. Because of the potential severity of infusion reactions, premedication with dexamethasone with the initial dose or with dose escalations or reinitiation of therapy is necessary. Blinatumomab should be administered under close medical observation and hospitalization for the first 9 days of therapy and for 2 days with subsequent cycles is recommended.

Hepatotoxicity

Serum aminotransferase elevations are common during blinatumomab therapy, yet are rarely discussed or mentioned in publications on its use in acute leukemia. In summary analyses of laboratory test abnormalities during blinatumomab therapy, ALT elevations were reported to occur in 93% of adult subjects and were above 5 times the upper limit of normal (ULN) in 36%. The elevations arose within the first few days of treatment during the first cycle and elevations were less common and lower with subsequent cycles. Rates of hyperbilirubinemia

were also high but all changes were reversible and there were no instances of clinically apparent liver injury attributable to the monoclonal therapy. Subsequent to its approval and more wide scale use, there have been no published instances of clinically apparent liver injury with jaundice attributable to blinatumomab therapy.

Likelihood score: E* (unproven but suspected cause of acute liver injury).

Mechanism of Injury

The mechanism by which blinatumomab causes liver injury is not known. It is a recombinant protein and unlikely to be inherently hepatoxic, being metabolized to small polypeptides or amino acids by many cells and having no effect on activity of drug metabolizing enzymes or hepatic transporter molecules. The serum enzyme abnormalities that are frequent during therapy may reflect a direct effect of the bispecific monoclonal antibody on hepatocytes or a secondary effect mediated by cytokine release from its action on malignant B cells. Because blinatumomab has effects on immune function and normal B cells, it may also be capable of causing reactivation of hepatitis B in susceptible patients, but instances of this adverse event have not been published.

Outcome and Management

Guidelines for management of patients who are to receive blinatumomab recommend routine monitoring of liver tests before and during blinatumomab therapy and interrupting treatment if serum aminotransferase levels rise above 5 times ULN or bilirubin above 3 times ULN. Mild-to-moderate elevations in serum aminotransferase levels are common during blinatumomab therapy, particularly in patients who develop cytokine release syndrome.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Blinatumomab – Blincyto®

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
Blinatumomab	853426-35-4	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 30 September 2017

Abbreviations used: ALL, acute lymphoblastic leukemia; HCT, hematopoietic cell transplantation.

Zimmerman HJ. Hepatotoxic effects of 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 published in 1999, well before the availability of most monoclonal antibody therapies).

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 rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; no specific discussion of blinatumomab).

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).

Handgretinger R, Zugmaier G, Henze G, Kreyenberg H, Lang P, von Stackelberg A. Complete remission after blinatumomab-induced donor T-cell activation in three pediatric patients with post-transplant relapsed acute lymphoblastic leukemia. Leukemia 2011; 25: 181-4. PubMed PMID: 20944674.

(3 children with refractory and relapsed B precursor ALL after HCT responded with complete remission after 4-6 weeks of infusions with blinatumomab with minimal adverse side effects).

Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, Horst HA, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011; 29: 2493-8. PubMed PMID: 21576633.

(Among 20 patients with relapsed ALL or with "minimal residual disease" who were treated with 59 cycles of blinatumomab, 16 had a molecular response but adverse events were frequent including lymphopenia, fever and hypokalemia, and one patient with transient ALT elevations above 5 times ULN).

Topp MS, Gökbuget N, Zugmaier G, Degenhard E, Goebeler ME, Klinger M, Neumann SA, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood 2012; 120: 5185-7. PubMed PMID: 23024237.

(After a median follow up of 33 months, 61% of the 20 patients with ALL treated with blinatumomab [Topp 2011], were still relapse-free and no further adverse events were reported).

Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, Seif AE, Nichols KE, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood 2013; 121: 5154-7. PubMed PMID: 23678006.

(Analysis of clinical features and cytokine levels in a patient with ALL treated with blinatumomab thought to be cytokine release syndrome was considered to be macrophage activation syndrome [MAS] and rapidly responded to toclizumab [anti-IL6] therapy).

Topp MS, Gökbuget N, Zugmaier G, Klappers P, Stelljes M, Neumann S, Viardot A, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol 2014; 32: 4134-40. PubMed PMID: 25385737.

(Among 36 patients with relapsed or refractory B-precursor ALL who were treated with blinatumomab, 69% achieved a complete response, and adverse events were common including fever [81%], fatigue [50%], headache [47%], tremor [36%] and leukopenia [19%]; no mention of ALT elevations or hepatotoxicity).

Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? Hepatology 2015; 61: 703-11. PubMed PMID: 25412906.

(Review of the pathogenesis, clinical course, treatment and prevention of HBV reactivation in patients receiving immunosuppressive or anticancer therapies, with particular focus on rituximab and ofatumumab; no mention of blinatumomab).

Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, Dombret H, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015; 16: 57-66. PubMed PMID: 25524800.

(Among 189 patients with refractory or relapsed B-precursor ALL treated with blinatumomab, 33% had a complete response, 2% had cytokine release syndrome, 11% neurological complications, and 13% had ALT elevations which were above 5 times ULN in 6%; no mention of clinically apparent hepatotoxicity).

Zugmaier G, Gökbuget N, Klinger M, Viardot A, Stelljes M, Neumann S, Horst HA, et al. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. Blood 2015; 126: 2578-84. PubMed PMID: 26480933.

(Among 36 adults with relapsed or refractor B-precursor ALL treated with blinatumomab, 10 [28%] were long term survivors and serious adverse events included convulsions, encephalopathy and cytokine release syndrome; no mention of ALT elevations or hepatotoxicity).

Viardot A, Goebeler ME, Hess G, Neumann S, Pfreundschuh M, Adrian N, Zettl F, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. Blood 2016; 127: 1410-6. PubMed PMID: 26755709.

(Among 21 patients with relapsed or refractory B-precursor ALL treated with blinatumomab, there were no liver related serious adverse events or deaths; ALT elevations were not reported).

Goebeler ME, Knop S, Viardot A, Kufer P, Topp MS, Einsele H, Noppeney R, et al. Bispecific T-Cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study. J Clin Oncol 2016; 34: 1104-11. PubMed PMID: 26884582.

(Among 76 patients with relapsed or refractory non-Hodgkin lymphoma treated with blinatumomab, neurologic events were dose limiting and at 60 μg/m2 per day, the overall response rate was 69%, neurologic adverse events occurred in 22% and ALT elevations in 33%, but none were above 5 times ULN).

Przepiorka D, Ko CW, Deisseroth A, Yancey CL, Candau-Chacon R, Chiu HJ, Gehrke BJ, Gomez-Broughton C, et al. FDA approval: blinatumomab. Clin Cancer Res 2015; 21: 4035-9. PubMed PMID: 26374073.

(Summary of the clinical studies that supported the FDA approval of blinatumomab for treatment of relapsed or refractory precursor B cell ALL; summary safety results from 212 treated adults mentions ALT elevations occurring in more than 10% of patients, but that "elevated transaminases generally occurred in the setting of cytokine release syndrome").

Blinatumomab (Blincyto) for acute lymphoblastic leukemia. Med Lett Drugs Ther 2015; 57 (1468): e74-5. PubMed PMID: 25941958.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of blinatumomab shortly after its approval in the US; no mention of ALT elevations or hepatotoxicity).

von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, Bader P, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016; 34: 4381-9. PubMed PMID: 27998223.

(Among 93 pediatric patients with relapsed or refractory ALL treated with varying doses of blinatumomab, 39% had a complete response to the optimal dose and the most frequent serious adverse events were anemia, thrombocytopenia and hypokalemia, while 4 patients had cytokine release syndrome and 2 seizures; ALT elevations above 5 times ULN occurred in 16%).

Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, Wei A, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017; 376: 836-47. PubMed PMID: 28249141.

(Among 405 patients with relapsed or refractory ALL treated with blinatumomab or standard chemotherapy, overall median survival was greater with blinatumomab [7.7 vs 4.0 months] and adverse events rates were similar [98.5% vs 99.1%]; although serious adverse events were higher with blinatumomab [62% vs 45%] but liver enzyme elevations were not [12.7% vs 14.7%]).

Burki TK. Blinatumomab significantly improves overall survival. Lancet Oncol 2017; 18: e203. PubMed PMID: 28285842.

(News report summarizing the controlled trial of blinatumomab that showed an improvement in overall survival in relapsed and refractory ALL [Kantarjian 2017]).

Nägele V, Kratzer A, Zugmaier G, Holland C, Hijazi Y, Topp MS, Gökbuget N, et al. Changes in clinical laboratory parameters and pharmacodynamic markers in response to blinatumomab treatment of patients with relapsed/refractory ALL. Exp Hematol Oncol 2017; 6: 14. PubMed PMID: 28533941.

(Among 36 adults with relapsed or refractory ALL treated with blinatumomab, ALT, AST and bilirubin levels rose within 24 hours of starting infusions and declined to baseline by the end of the cycle, but rose minimally with subsequent cycles, elevations being mild-to-moderate in degree and fully reversible, corresponding to the timing of cytokine release).