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Lomustine

Updated: June 3, 2019.

OVERVIEW

Introduction

Lomustine is an orally administered alkylating agent used alone and in combination with other antineoplastic agents in the treatment of several malignancies including Hodgkin disease, lymphoma, and brain cancer. Lomustine therapy is associated with minor transient serum enzyme elevations and has been linked to rare cases of clinically apparent acute liver injury.

Background

Lomustine (loe mus' teen: also known as CCNU) is a nitrosourea similar to carmustine (BCNU), which acts as an alkylating agent and is used in the therapy of several forms of lymphoma and solid organ cancer. Like cyclophosphamide, lomustine requires activation in the liver to form its active intermediaries which act by modifying and cross linking purine bases in DNA, thus inhibiting DNA, RNA and protein synthesis and leading to programmed cell death (apoptosis) in rapidly dividing cells. Lomustine also forms adducts with cellular proteins. Lomustine was approved for use in the United States in 1977, and its current indications include treatment of brain cancer, and Hodgkin and non-Hodgkin lymphomas. Lomustine is available as capsules of 10, 40 and 100 mg in generic forms and under the trade name CeeNU. Recommended doses vary by age, body weight and malignant condition. Lomustine is usually given in combination with other antineoplastic agents in a single oral dose of 100-130 mg/m^2 in cycles every 6 to 8 weeks. The toxicity of lomustine is similar to other alkylating agents. Common side effects include alopecia, nausea, vomiting, diarrhea, gastrointestinal upset, nephrotoxicity, oral ulcers and bone marrow suppression.

Hepatotoxicity

Mild and transient elevations in serum aminotransferase or alkaline phosphatase levels are found in a high proportion of patients treated antineoplastic regimens that include lomustine. The abnormalities are generally transient, do not cause symptoms and do not require dose modification. Clinically apparent liver injury from lomustine has been described, but is uncommon. The pattern of serum enzyme elevations were described as cholestatic and onset was after 3 to 4 months of therapy, but otherwise its clinical characteristics have not been clearly characterized. Lomustine is often given in combination with other antineoplastic agents, many of which are also hepatotoxic, so the effect of lomustine in causing liver injury is often difficult to assess. Lomustine has not been associated specifically with sinusoidal obstruction syndrome, but it is not generally given in high doses or used for myeloablation in preparation for bone marrow transplantation, the situations in which this syndrome generally occurs.

Likelihood score: D (possible cause of clinically apparent liver injury).

Mechanism of Injury

The cause of idiosyncratic hepatotoxicity from lomustine is not known. Lomustine is extensively metabolized by hepatic cytochrome P450 system.

Outcome and Management

The severity of liver injury ranges from mild elevations in liver enzymes to mild and self limited cholestatic liver injury. It is not known whether patients with acute liver injury due to lomustine have cross sensitivity to hepatic injury with other alkylating agents.

Drug Class: Antineoplastic Agents, Alkylating Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lomustine – CeeNU®

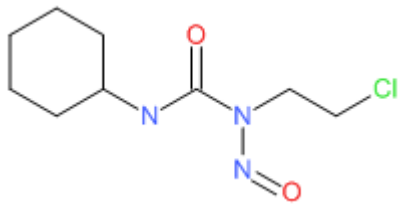
DRUG CLASS

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
Lomustine	13010-47-4	C9-H16-Cl-N3-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 03 June 2019

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; mentions that lomustine has been linked to serum aminotransferase elevations).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 541-67.

(Review of hepatotoxicity of cancer chemotherapeutic agents; lomustine is listed as an uncommon cause of liver injury but capable of causing sinusoidal obstruction syndrome at high doses).

Wellstein A, Giaconne G, Atkins MB, Sausville EA. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 20181, pp. 1167-1201.

(Textbook of pharmacology and therapeutics).

De Vita VT, Carbone PP, Owens AH Jr, Gold GL, Krant MJ, Edmonson J. Clinical trials with 1,3-bis (2-chloroethyl)-1-nitrosourea, NSC-409962. Cancer Res 1965; 25: 1876-81. PubMed PMID: 5858571.

(Preliminary studies of BCNU in 144 patients with malignancies, including different dose schedules; AST elevations occurred in 15% after 13-63 days and were self-limited in all; liver toxicity may have contributed to the death of one patient).

Hansen HH, Selawry OS, Muggia FM, Walker MD. Clinical studies with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037). Cancer Res 1971; 31: 223-7. PubMed PMID: 4926242.

(Preliminary studies of CCNU in 40 patients with malignancies; there was no consistent hepatic dysfunction; AST elevations occurred in one patient).

Lokich JJ, Drum DE, Kaplan W. Hepatic toxicity of nitrosourea analogues. Clin Pharmacol Ther 1974; 16: 363-7. PubMed PMID: 4852251.

(2 cases: 70 year old man with metastatic colon cancer and cirrhosis developed jaundice 6 weeks after a 5 day course of carmustine and streptozotocin [bilirubin 6.2 mg/dL, but no other information given]; 66 year old man with pancreatic cancer developed jaundice 2 weeks after carmustine and streptozotocin [bilirubin 3.5 mg/dL, AST 30 U/L, Alk P 135 U/L], with recovery after stopping).

Lessner HE, Vogler WR. Toxicity study of BCNU (NSC-409965) given orally. Cancer Chemother Rep 1974; 58: 407-11. PubMed PMID: 4601671.

(Pilot study of carmustine alone in various oral doses in 104 patients with cancer; two patients developed liver toxicity, one with jaundice and elevated Alk P, but relationship to drug was uncertain).

de Labarthe B, Chahinian P, Gosselin M, Goasguen J, Ferrand B, Danrigal A, Israel L. [Hepatic damage during treatment with C.C.N.U]. Sem Hop Ther 1975; 51: 309-14. French. PubMed PMID: 1224203.

(50 year old woman with metastatic breast cancer developed jaundice during the fourth month of lomustine monotherapy [every 3 weeks], with bilirubin rising to 10.1 mg/dL, ALT 2900 U/L and Alk P 3-4 times ULN, ultimately recovered but died of metastatic disease several months later).

Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, Vogelsang GB, et al. Veno-occlusive disease of the liver following bone marrow transplantation. Transplantation 1987; 4: 778-83. PubMed PMID: 3321587.

(Among 235 patients undergoing bone marrow transplantation between 1982 and 1985, sinusoidal obstruction syndrome [SOS] developed in 52 [22%] of whom half died, making SOS the third most common cause of death in this population).

Kim L, Hochberg FH, Thornton AF, Harsh GR 4th, Patel H, Finkelstein D, Louis DN. Procarbazine, lomustine, and vincristine (PCV) chemotherapy for grade III and grade IV oligoastrocytomas. J Neurosurg 1996; 85: 602-7. PubMed PMID: 8814163.

(Among 32 pateitns with astrocytotoma treated with a total of 124 cycles of procarbazine, lomustine and vincristine, there "were no reports of hepatic toxicity" and most dose adjustments were for hematologic toxicities).

McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology 2010; 51: 1450-60. PubMed PMID: 20373370.

(Review of liver complications of bone marrow [hematopoietic cell] transplantation, which have become less frequent with better understanding of their causes and means of prevention; the rate of sinusoidal obstruction syndrome has decreased because of avoidance of more aggressive ablative therapies [total body irradiation and high doses of cyclophosphamide] and better understanding of pharmacokinetics of the alkylating agents; lomustine is not specifically discussed).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, 40 of which were attributed to antineoplastic agents, but none specifically to lomustine).

Douros A, Bronder E, Andersohn F, Klimpel A, Thomae M, Sarganas G, Kreutz R, et al. Drug-induced liver injury: results from the hospital-based Berlin Case-Control Surveillance Study. Br J Clin Pharmacol 2015; 79: 988-99. PubMed PMID: 25444550.

(Among 198 patients with hepatitis of uniknown cause enrolled in a prospective database from 51 Berlin hospitals between 2002 and 2011, none were attributed to lomustine).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 cases were attributed to antineoplastic agents, but none to lomustine).

Jutras G, Bélanger K, Letarte N, Adam JP, Roberge D, Lemieux B, Lemieux-Blanchard É, et al. Procarbazine, lomustine and vincristine toxicity in low-grade gliomas. Curr Oncol 2018; 25: e33-e39. PubMed PMID: 29507493.

(Among 57 patients treated with a regimen of procarbazine, lomustine and vincristine for low grade gliomas between 2005 and 2016, hematologic, hepatic and renal toxicities were common, ALT elevations arising in 65% of patients which were above 5 times ULN in 18%, but the major dose limiting toxicities were hematologic).