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Ifosfamide

Updated: April 15, 2018.

OVERVIEW

Introduction

Ifosfamide is a parenterally administered alkylating agent similar to cyclophosphamide that is used in the treatment of several forms of cancer including lymphomas, sarcoma and advanced forms of solid organ cancer such as breast, testicular, ovarian, gastric and lung cancer. Ifosfamide therapy is associated with minor transient serum enzyme elevations and has been linked to cases of acute liver injury, including acute cholestatic hepatitis and veno-occlusive disease.

Background

Ifosfamide (eye fos' fa mide) is an analogue of cyclophosphamide and thus a nitrogen mustard-like alkylating agent that is used in the therapy of several forms of leukemia, lymphoma and solid organ cancer. Like cyclophosphamide, ifosfamide 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. Ifosfamide was approved for use in the United States in 1988 and its major indication is for germ cell testicular cancer, but it is also used in combination with other agents in the treatment of breast, lung, bladder, cervical, and ovarian cancer, Hodgkin's and non-Hodgkin's lymphoma, and soft tissue and osteogenic sarcomas. Ifosfamide is given intravenously and is available in liquid formulations (1 and 3 gram vials), generically and under the trade name Ifex. Recommended doses vary by body weight and malignant condition. Common side effects include alopecia, nausea, vomiting, diarrhea, gastrointestinal upset, cystitis, oral ulcers and bone marrow suppression. It is commonly given with mesna to reduce the risk of hemorrhagic cystitis.

Hepatotoxicity

The toxicity of ifosfamide seems to be similar to that of cyclophosphamide. Mild and transient elevations in serum aminotransferase levels are found in a high proportion of patients receiving ifosfamide. Because ifosfamide is typically given in combination with other antineoplastic agents, its role in causing the serum enzyme elevations is often not clear. The abnormalities are generally transient, do not cause symptoms and do not require dose modification. Clinically apparent liver injury from ifosfamide has been limited to a small number of cases of cholestatic hepatitis arising within a few weeks of receiving ifosfamide (with other antineoplastic agents). In addition, sinusoidal obstruction syndrome has been reported after conditioning regimens that have included ifosfamide in preparation for hematopoietic cell transplantation. The onset of injury is usually within one to three weeks of the myeloablation and is characterized by a sudden onset of abdominal pain, weight gain, ascites, marked increase in serum aminotransferase levels (and lactic dehydrogenase), and

subsequent jaundice and hepatic dysfunction. The severity of sinusoidal obstruction syndrome varies from a transient, self limited injury to acute liver failure. The diagnosis is usually based on clinical features of tenderness and enlargement of the liver, weight gain, ascites and jaundice. Liver biopsy is diagnostic but often contraindicated, because of severe thrombocytopenia after bone marrow transplantation.

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

Mechanism of Injury

The cause of idiosyncratic hepatotoxicity from ifosfamide is not known. The sinusoidal obstruction syndrome induced by ifosfamide is probably related to the direct toxic effect of ifosfamide on sinusoidal cells in the liver, causing their necrosis and release into the sinusoids, obstruction and obliteration of hepatic veins. Ifosfamide is extensively metabolized by hepatic cytochrome P450 system and more than 150 metabolites have been identified, but their pharmacokinetics and toxicities are not well defined.

Outcome and Management

The severity of liver injury ranges from mild elevations in liver enzymes to massive, fatal hepatic necrosis due to sinusoidal obstruction syndrome. There is currently no specific therapy for veno-occlusive disease other than supportive management and avoidance of further damage. Rechallenge should be avoided.

Drug Class: Antineoplastic Agents, Alkylating Agents, see also Cyclophosphamide

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ifosfamide – Generic, Ifex®

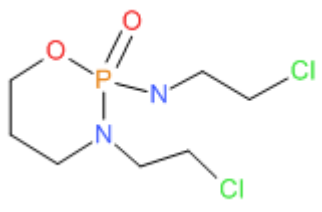
DRUG CLASS

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
Ifosfamide	3778-73-2	C7-H15-Cl2-N2-O2-P	

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2018.

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 a report of two cases of cholestatic injury in patients receiving both ifosfamide and etoposide [Paschke 1988]).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 551. *(Review of hepatotoxicity of cancer chemotherapeutic agents mentions that cyclophosphamide is an uncommon cause of liver injury, but in high doses in combination with busulfan or irradiation, can cause sinusoidal obstruction syndrome;*

ifosfamide is not separately discussed).

Chabner BA, Bertino J, Cleary J, Ortiz T, Lane A, Supko JG, Ryan D. Cytotoxic agents. 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: ifosfamide is a analogue of cyclophosphamide that is given intravenously and is a common component of high dose chemotherapy regimens with hematopoietic cell transplantation).

Paschke R, Worst P, Brust J, Queisser W. [Hepatotoxicity with etoposide-ifosfamide combination therapy]. Onkologie 1988; 11: 273-5. German. PubMed PMID: 2853857.

(Two patients treated for bronchogenic carcinoma; 57 year old man developed liver injury [bilirubin 2.7 rising to 22.6 mg/dL, AST 27 U/L, Alk P 225 U/L] 10 days after receiving etoposide and isofosfamide; 68 year old woman developed jaundice after a third course of etiopsomide with ifosfamide [bilirubin 6.5 rising to 12.3 mg/dL, AST 39 U/L, Alk P 218 U/L]).

Cheung MC, Jones RL, Judson I. Acute liver toxicity with ifosfamide in the treatment of sarcoma: a case report. J Med Case Rep 2011; 5: 180. *(61 year old woman with inoperable synovial sarcoma developed confusion 3 days after completing chemotherapy with doxorubicin, dexamethasone and ifosfamide [bilirubin 2.1 mg/dL, ALT 3086 U/L, Alk P 77 U/L, INR 2,2, ammonia 77 μ* PubMed PMID: 21569511.

M/L] recovering within two weeks and later tolerating doxorubicin without recurrence).

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 Citation (Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, one of which was attributed to cyclophosphamide but none to ifosfamide).

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 Citation

(Among 198 patients with suspected drug induced liver injury enrolled in a case control surveillance study involving 51 hospitals in Berlin between 2002 and 2011, one case was considered probably due to cyclophosphamide but none to ifosfamide).

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 Citation

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 cases [6%] were attributed to antineoplastic agents, 2 of which were due to cyclophosphamide but none to ifosfamide).

Fan XL, Cai GP, Zhu LL, Ding GM. Efficacy and safety of ifosfamide-based chemotherapy for osteosarcoma: a meta-analysis. Drug Des Devel Ther 2015; 9: 5925-32. PubMed PMID: 26604690.

(Systematic review of literature on use of ifosfamide for osteosarcoma concluded that it significantly improved event-free survival while adverse reactions included fever, nausea, cardiotoxicity, CNS toxicity, skin rash and myelosuppression; no mention of ALT elevations or hepatotoxicity).