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Thiotepa

Updated: December 12, 2013.

OVERVIEW

Introduction

Thiotepa is an intravenously or locally applied or injected alkylating agent which is currently used in the therapy of breast, ovarian and bladder cancer and for Hodgkin disease. Thiotepa therapy has been associated with low rates of serum enzyme elevations during therapy and very rare instances of acute, clinically apparent injury.

Background

Thiotepa (thye' oh tep' a) is an ethylenimine similar in structure and activity to altretamine and is believed to act as an alkylating agent. The alkylating agents act by causing modification and cross linking of DNA, thus inhibiting DNA, RNA and protein synthesis and causing programmed cell death (apoptosis) in rapidly dividing cells. Thiotepa was approved for use in the United States in 1959. Current indications include ovarian and breast cancer and Hodgkin disease. Thiotepa is also administered locally for bladder cancer, neoplastic effusions and malignant meningeal neoplasms. Thiotepa is available generically in vials of 15 mg. The recommended dose varies by indications, route of administration, and body weight. Thiotepa shares common side effects with other alkylating agents such as nausea, vomiting, diarrhea, alopecia, bone marrow suppression, rash and hypersensitivity reactions.

Hepatotoxicity

Thiotepa therapy is associated with a low rate of serum enzyme elevations, but these are generally mild and self limited, not requiring dose adjustment. Rare instances of clinically apparent acute liver injury attributed to thiotepa have been reported, particularly with high doses. In most instances, thiotepa was administered in combination with other agents known to cause liver injury and the specific role of thiotepa was not clear. Thiotepa is often used in combination with other alkylating agents in conditioning regimens for bone marrow ablation in preparation for hematopoietic cell transplantation and as such has been linked to instances of sinusoidal obstruction syndrome. Onset of sinusoidal obstruction syndrome is usually within 1 to 3 weeks of myeloablative or high dose therapy and is characterized by the sudden development of abdominal pain, hepatomegaly, weight gain and ascites followed by jaundice. The pattern of serum enzyme elevations is usually hepatocellular, with marked increases in serum aminotransferase and lactic dehydrogenase levels and minimal increase in alkaline phosphatase. In severe instances, there are elevations in prothrombin time and progressive hepatic failure. Immunoallergic and autoimmune features are uncommon. The fatality rate is high. Liver biopsy shows centrolobular necrosis and congestion with occlusion of small veins and red cells in sinusoids.

Mechanism of Injury

The potential mechanism of hepatotoxicity from thiotepa is probably similar to that of other alkylating agents, a direct cytotoxic injury to rapidly dividing cells. High doses are likely to injure other cells such as sinusoidal endothelial cells and hepatocytes. The cause of the idiosyncratic liver injury associated with thiotepa is not known.

Outcome and Management

Liver injury is not uncommon with high doses of thiotepa. The severity of injury in reported cases has generally been mild-to-moderate and self limited in course, although fatalities attributed to hepatotoxicity have been reported. The sinusoidal obstruction syndrome associated with thiotepa and other alkylating agents can be severe and lead to acute liver failure. There have been no instances of chronic hepatitis or vanishing bile duct syndrome definitely linked to thiotepa therapy. In situations of acute liver injury after thiotepa use, rechallenge should be avoided.

Drug Class: Antineoplastic Agents, Alkylating Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Thiotepa – Generic, Thioplex®

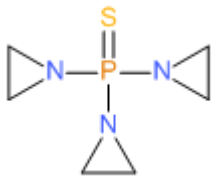
DRUG CLASS

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
Thiotepa	52-24-4	C6-H12-N3-P-S	

ANNOTATED BIBLIOGRAPHY

References updated: 12 December 2013

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; thiotepa has been implicated in at least one case of acute liver failure).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 549-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents).

Chabner BA, Bertino J, Clearly J, Ortiz T, Lane A, Supko JG, Ryan DP. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1315-404.

(Textbook of pharmacology and therapeutics).

Rollins BJ. Hepatic veno-occlusive disease. Am J Med 1986; 8: 297-306. PubMed PMID: 3526887.

(Review of the diagnosis, clinical course, histology and pathogenesis of veno-occlusive disease).

Lazarus HM, Reed MD, Spitzer TR, Rabaa MS, Blumer JL. High-dose i.v. thiotepa and cryopreserved autologous bone marrow transplantation for therapy of refractory cancer. Cancer Treat Rep 1987; 71: 689-95. PubMed PMID: 3111687.

(Among 25 patients with refractory cancers treated with escalating doses of thiotepa followed by autologous bone marrow transplantation, toxicity was dose limiting and 2 had hepatotoxicity, one being fatal, but no details given).

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 hematopoietic cell 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).

Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. Blood 1995; 85: 3005-20. PubMed PMID: 7756636.

(Review of SOS after hematopoietic cell transplantation; usually presents with painful hepatomegaly, weight gain [fluid and ascites] and jaundice within 3 weeks of myeloablation with occlusion of central veins and sinusoids and extensive zone 3 [centrolobular] injury).

Przepiorka D, Nath R, Ippoliti C, Mehra R, Hagemeister F, Diener K, Dimopoulos M, et al. A phase I-II study of high-dose thiotepa, busulfan and cyclophosphamide as a preparative regimen for autologous transplantation for malignant lymphoma. Leuk Lymphoma 1995; 17: 427-33. PubMed PMID: 7549833.

(Among 34 patients with lymphoma treated with high dose thiotepa, busulfan and cyclophosphamide with autologous hematopoietic cell transplantation, liver toxicity was common at high doses, 3 developing "centrilobular necrosis" without SOS).

Papadakis V, Dunkel IJ, Cramer LD, Kramer E, Papadopoulos E, Goldman S, Packer RJ, et al. High-dose carmustine, thiotepa and etoposide followed by autologous bone marrow rescue for the treatment of high risk central nervous system tumors. Bone Marrow Transplant 2000; 26: 153-60. PubMed PMID: 10918425.

(Among 42 patients with brain tumors who were treated with high dose carmustine, thiotepa and etoposide and autologous hematopoietic cell transplantation, 2 developed SOS and 5 had transient elevations in ALT levels).

Lee JL, Gooley T, Bensinger W, Schiffman K, McDonald GB. Veno-occlusive disease of the liver after busulfan, melphalan, and thiotepa conditioning therapy: incidence, risk factors, and outcome. Biol Blood Marrow Transplant 1999; 5: 306-15. PubMed PMID: 10534061.

(Among 253 patients who received a regimen of busulfan, melphalan and thiotepa in preparation for hematopoietic stem cell transplantation, 70 [28%] developed SOS, which was severe in 11 and fatal in 9).

DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome. Semin Liver Dis 2002; 22: 27-41. PubMed PMID: 11928077.

(Review of clinical features, pathology, etiology, prevention and treatment of sinusoidal obstruction syndrome, a better term for this condition than veno-occlusive disease; first described in association with exposure to phytotoxins [pyrrolizidine alkaloids], the most common cause now is cancer chemotherapy and particularly myeloablative conditioning regimens in preparation for bone marrow transplantation).

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).