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Procarbazine

Updated: January 23, 2014.

OVERVIEW

Introduction

Procarbazine is an orally administered alkylating agent used in combination with other anti-neoplastic agents in the therapy of Hodgkin's disease and malignant melanoma. Procarbazine therapy has been associated with serum enzyme elevations during therapy and with rare cases of idiosyncratic, clinically apparent acute liver injury.

Background

Procarbazine (proe kar' ba zeen) is a methylhydrazine derivative which is activated in the liver to highly reactive alkylating intermediates. These intermediates methylate DNA which causes inhibition of DNA, RNA and protein synthesis and cell death. Procarbazine was approved for use in the United States in 1969 and it remains a commonly used agent in the treatment of Hodgkin's and non-Hodgkin's lymphomas and brain cancer. Procarbazine is rarely used alone, but is found in common cancer chemotherapeutic regimens such as MOPP (mechlorethamine, vincristine [oncovin], procarbazine and prednisone), COPP (cyclophosphamide, vincristine [oncovin], procarbazine and prednisone), and PCV (procarbazine, lomustine [CCNU], vincristine). Procarbazine is available as tablets of 50 mg generically and under the brand name Matulane. It is typically given in monthly or every other month cycles of 10 to 14 days in a dose of 100 mg per meter squared body surface area. Common side effects are alopecia, anoxia, nausea, vomiting, headache, peripheral neuropathy, and flu-like illness.

Hepatotoxicity

Mild and transient elevations in serum aminotransferase levels are not uncommon during courses of systemic combination chemotherapy and the role of procarbazine in these abnormalities is often not clear. However, dose modification for serum enzyme elevations is rarely necessary. Clinically apparent liver disease with fever and marked elevations in serum aminotransferase levels without jaundice has been reported but is very rare.

Mechanism of Injury

The mechanism of hepatotoxicity from procarbazine is not known, but may be due to hypersensitivity.

Outcome and Management

The severity of liver injury from procarbazine is usually mild and self limiting. Procarbazine therapy has not been associated with cases of acute liver failure, chronic liver injury or vanishing bile duct syndrome. A single

case report described self-limited, hepatocellular injury without jaundice during a second course of combination therapy and recurrence upon rechallenge with procarbazine, but not with the other antineoplastic agents being used.

Drug Class: Antineoplastic Agents, Alkylating Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Procarbazine – Matulane®

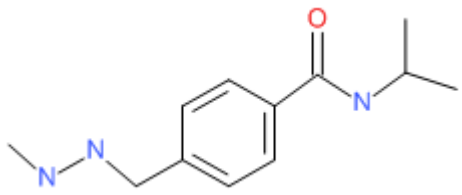
DRUG CLASS

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
Procarbazine	671-16-9	C12-H19-N3-O	

ANNOTATED BIBLIOGRAPHY

References updated: 23 January 2014

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 procarbazine appears to produce little hepatic injury, and its other side effects outweigh the importance of its hepatotoxicity).

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 does not discuss procarbazine).

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).

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).

Fesler MJ, Becker-Koepke S, Di Bisceglie AM, Petruska PJ. Procarbazine-induced hepatotoxicity: case report and review of the literature. Pharmacotherapy 2010; 30: 540. PubMed PMID: 20412004.

(65 year old man with lymphoma developed fever and transient marked elevations in ALT [~2100 U/L] and LDH [873 U/L] during second course of C-MOPP-R and had a positive rechallenge to procarbazine [fever and ALT elevations to ~800 U/L], but no recurrence with other components of the treatment regimen).