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Decitabine

Updated: December 27, 2017.

OVERVIEW

Introduction

Decitabine is a cytosine analogue and an intravenously administered antineoplastic agent used in the therapy of myelodysplastic syndromes. Decitabine is associated with a low rate of transient serum enzyme elevations during therapy, but has not been implicated in causing clinically apparent liver injury with jaundice.

Background

Decitabine (dee sye' ta been) is a pyrimidine analogue (5-aza-deoxy-cytidine) which is the deoxyribose form of 5-azacitidine. Decitabine is converted intracellularly to a triphosphate which becomes incorporated into DNA and appears to inhibit DNA methylation, resulting in increased expression of silenced genes including tumor suppressor genes. Studies done in vitro and in vivo have shown that decitabine induces differentiation of bone marrow cells and results in normalization of bone marrow in a proportion of patients with myelodysplasia. Decitabine was approved for use in the United States in 2006 and the current single indication is for therapy of myelodysplasic syndromes. Decitabine is available as a powder or solution for injection in 50 mg vials under the trade name of Dacogen. The usual dosage regimen in adults is 15 to 20 mg per meter-squared body surface area given intravenously in several day regimens, with repeat cycles every 4 or 6 weeks. A minimum of 4 courses is recommended. Common side effects include bone marrow suppression, nausea, vomiting, diarrhea, stomatitis, bruising, abdominal pain, myalgias, headache, dizziness, fatigue, fever, rash and pruritus.

Hepatotoxicity

In early clinical trials using high doses of decitabine, serum enzyme elevations occurred in up to 16% of patients with underlying liver disease or liver metastases, but rarely in persons without hepatic illness. In subsequent studies, serum ALT elevations were reported in 5% to 15% of treated patients, but all were self-limited and no clinically apparent liver injury was reported. Recent studies have reported elevations in serum bilirubin levels in 7% to 12% of treated patients, but the elevations resolved rapidly and were not associated with other clinical or laboratory evidence of liver injury. Monitoring of serum enzyme levels during treatment is recommended only in patients with concurrent liver disease.

Likelihood score: E* (unproven but suspected, rare cause of clinically apparent liver injury).

Mechanism of Injury

Hepatotoxicity from decitabine appears to be rare and confined mostly to patients with underlying liver disease. Thus, the liver injury is likely due to direct toxicity which is generally minimal or mild except in susceptible patients.

Outcome and Management

The severity of the liver injury linked to decitabine therapy is usually mild to moderate in severity, occurring in patients with preexisting liver disease. Decitabine has not been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no information on cross sensitivity to hepatic injury between decitabine and other cytidine analogues including azacitidine.

Drug Class: Antineoplastic Agents

Other Drugs in the Subclass, Pyrimidine Analogues: Azacitidine, Capecitabine, Cytarabine, Floxuridine, Fluorouracil, Gemcitabine, Trifluridine/Tipracil

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Decitabine – Dacogen®

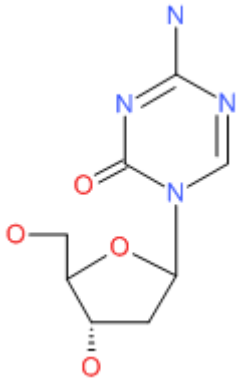
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Decitabine	2353-33-5	2353-33-5	

ANNOTATED BIBLIOGRAPHY

References updated: 27 December 2017

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 of cancer chemotherapeutic agents published in 1999; decitabine is not discussed).

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

(Review of hepatotoxicity of cancer chemotherapeutic agents; decitabine is not discussed).

Chabner BA, Bertino J, Cleary 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. 1677-739.

(Textbook of pharmacology and therapeutics).

Wijermans PW, Lü M, Verhoef G, Klimek V, Bosly A. An epigenetic approach to the treatment of advanced MDS; the experience with the DNA demethylating agent 5-aza-2'-deoxycytidine (decitabine) in 177 patients. Ann Hematol 2005; 84Suppl 1: 9-17. PubMed PMID: 16211386.

(Pooled results of 3 European trials of decitabine in 177 patients with myelodysplasia; response rate was 49%, liver enzyme elevations occurred in 16% of patients in one study and "liver toxicity" was reported in 1% of patients in another, but no case of clinically apparent liver injury or death from liver disease was reported).

Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, Klimek V, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer 2006; 106: 1794-803. PubMed PMID: 16532500.

(Among 170 patients with myelodysplasia treated with decitabine vs standard of care, hyperbilirubinemia occurred in 7% on decitabine vs none receiving standard care; no mention of ALT elevations).

Kantarjian H, Oki Y, Garcia-Manero G, Huang X, O'Brien S, Cortes J, Faderl S, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood 2007; 109: 52-7. PubMed PMID: 16882708.

(95 patients with severe myelodysplasia or chronic leukemia were randomized to 3 regimens of decitabine [iv or sc for 5 days, or iv at half dose for 10 days]; ALT elevations occurred in 14 patients [15%] and were above 5 times ULN in 4 [4%], but all resolved and none required dose modification or discontinuation).

Aribi A, Borthakur G, Ravandi F, Shan J, Davisson J, Cortes J, Kantarjian H. Activity of decitabine, a hypomethylating agent, in chronic myelomonocytic leukemia. Cancer 2007; 109: 713-7. PubMed PMID: 17219444.

(Among 19 patients with chronic leukemia treated with decitabine intravenously or subcutaneously for 5-10 days every 4 weeks, one had ALT elevations above 5 times ULN, but "non-hematologic side effects were minimal").

Jabbour E, Issa JP, Garcia-Manero G, Kantarjian H. Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. Cancer 2008; 112: 2341-51. PubMed PMID: 18398832.

(Review of structure, mechanism of action, pharmacokinetics, efficacy in various conditions and safety of decitabine; hyperbilirubinemia occurred in up to 12% of patients receiving decitabine, but ALT elevations and cause of bilirubin rise were not discussed).

Steensma DP, Baer MR, Slack JL, Buckstein R, Godley LA, Garcia-Manero G, Albitar M, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol 2009; 27: 3842-8. PubMed PMID: 19528372.

(Among 99 patients with myelodysplasia treated with decitabine [20 mg/m^2] daily for 5 days every 28 days, one patient died of hepatic failure, but no details given).

Garcia JS, Jain N, Godley LA. An update on the safety and efficacy of decitabine in the treatment of myelodysplastic syndromes. Onco Targets Ther 2010; 3: 1-13. PubMed PMID: 20616953.

(Systematic review of safety and efficacy of decitabine in myelodysplasia; liver dysfunction is reported in 1-11% of patients, but details not provided or discussed).

Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, Gau JP, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012; 30: 2670-7. PubMed PMID: 22689805.

(Among 485 patients with AML treated with decitabine, cytarabine or supportive care, adverse events were similar with decitabine and cytarabine; no discussion of ALT elevations or liver injury).

Lee YG, Kim I, Yoon SS, Park S, Cheong JW, Min YH, Lee JO, et al. Comparative analysis between azacitidine and decitabine for the treatment of myelodysplastic syndromes. Br J Haematol 2013; 161: 339-47. PubMed PMID: 23432512.

(Observational study comparing safety and efficacy of azacitidine vs decitabine in 300 Korean patients with myelodysplasia, found similar rates of efficacy and side effects; no mention of ALT elevations or hepatotoxicity).

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 [5.5%] were attributed to antineoplastic agents, but none were linked to decitabine treatment).

Salim O, Toptas T, Avsar E, Yucel OK, Ozturk E, Ferhanoglu B, Geduk A, et al. Azacitidine versus decitabine in patients with refractory anemia with excess blast-results of multicenter study. Leuk Res 2016; 45: 82-9. PubMed PMID: 27107658.

(Among 88 patients with refractory anemia treated with azacitidine or decitabine followed at 6 Turkish referral centers, overall survival, transfusion requirements and rates of adverse events and acute leukemia were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Nieto M, Demolis P, Béhanzin E, Moreau A, Hudson I, Flores B, Stemplewski H, et al. The European Medicines Agency review of decitabine (Dacogen) for the treatment of adult patients with acute myeloid leukemia: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. Oncologist 2016; 21: 692-700. PubMed PMID: 27091416.

(Review of the efficacy and safety of decitabine by a European expert panel concluded that its use should be limited to adults over the age of 65 with AML who are not candidates for standard induction therapy; and that adverse events are similar to those of low dose cytarabine, largely due to myelosuppression; no mention of ALT elevations or hepatotoxicity).

Jabbour E, Short NJ, Montalban-Bravo G, Huang X, Bueso-Ramos C, Qiao W, Yang H, et al. Randomized phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN. Blood 2017; 130: 1514-22. PubMed PMID: 28774880.

(Among 113 patients with lower-risk myelodysplastic syndromes treated with low doses of azacitine or decitabine, overall response rates favored decitabine [70% vs 49%], as did rates of transfusion independence and cytogenetic responses, and both therapies were "overall well tolerated"; no mention of ALT elevations or hepatotoxicity).