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Azacitidine

Updated: August 2, 2017.

OVERVIEW

Introduction

Azacitidine is a cytosine analogue and antineoplastic agent used in the therapy of myelodysplastic syndromes. Azacitidine is associated with a low rate of transient serum enzyme elevations during therapy and has only rarely been implicated in cases of clinically apparent acute liver injury with jaundice.

Background

Azacitidine (ay" za sye' ti deen: also spelled azacytidine) is a pyrimidine analogue (5-azacytidine) which is converted intracellularly to a triphosphate which becomes incorporated into RNA and DNA. While azacitidine has anticancer effects, it proved to have limited usefulness in solid tumors and lymphomas. In low doses, azacitidine inhibits methylation of DNA and results in the expression of silenced genes, including tumor suppressor genes. Studies done in vitro and in vivo have shown that azacitidine induces differentiation of bone marrow cells and results in normalization of bone marrow in a proportion of patients with myelodysplasia. Azacitidine was approved for use in the United States in 2004 and the current single indication is for therapy of myelodysplastic syndromes. It is also under evaluation as therapy of acute myelogenous leukemia. Azacitidine is available as a powder for injection in 100 mg vials under the trade name of Vidaza. An oral formulation is currently under evaluation. The usual initial dosage regimen in adults is 75 mg per meter-squared body surface area subcutaneously each day for 7 days, with repeat courses after 28 days. A minimum of 4 courses is recommended and the dose can be increased based upon tolerance and response. Common side effects include bone marrow suppression, nausea, vomiting, diarrhea, stomatitis, bruising, abdominal pain, myalgias, headache, dizziness, fatigue, fever, rash and pruritus.

Hepatotoxicity

In clinical trials, serum enzyme elevations occurred in up to 16% of patients on azacitidine therapy for cancer or myelodysplasia who had concurrent, underlying liver disease or liver metastases, but rarely in persons without a preexisting hepatic illness. In subsequent studies, liver adverse reactions attributed to azacitidine have rarely been reported, at least when it is given in conventional doses. Nevertheless, monitoring of serum enzyme levels is recommended in treating patients who have concurrent liver disease. Cases of clinically apparent liver injury attributed to azacitidine in patients without underlying liver disease have not been reported in the literature.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury in persons with pre-existing liver disease).

Mechanism of Injury

Hepatotoxicity from azacitidine appears to be rare and confined mostly to patients with underlying liver disease. For these reasons, the liver injury is likely due to direct toxicity.

Outcome and Management

The severity of the liver injury linked to azacitidine therapy is usually mild to moderate in severity occurring in patients with preexisting liver disease. Azacitidine 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 azacitidine and other nucleoside or cytidine analogues.

Drug Class: Antineoplastic Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Azacitidine – Vidaza®

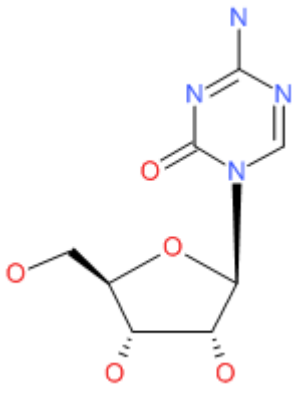
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Azacitidine	320-67-2	C8-H12-N4-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 02 August 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; mentions that azacitidine can cause serum aminotransferase elevations, but has been considered not very hepatotoxic).

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

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

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, Longo DL, Mitsiades C, Richardson P. 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 states that azacitidine like decitabine induce differentiations of cells by inhibition of DNA cytosine methyltransferase activity and both are used to treat myelodysplasia).

Weiss AJ, Stambaugh JE, Mastrangelo MJ, Laucius JF, Bellet RE. Phase I study of 5-azacytidine(NSC-102816). Cancer Chemother Rep 1972; 56: 413-9. PubMed PMID: 19051503.

(Among 30 patient with advanced malignancies treated with azacitidine [0.5 to 1.4 mg/kg/day] for 10-15 days, reversible rises in AST but no other liver abnormalities occurred in several patients).

Bellet RE, Mastrangelo MJ, Engstrom PF, Custer RP. Hepatotoxicity of 5-azacytidine (NSC-102816) (a clinical and pathologic study). Neoplasma 1973; 20: 303-9. PubMed PMID: 4125219.

(Among 20 patients with various malignancies treated with azacitidine [0.8-2.2 mg/kg/day] for 10 days, liver adverse events occurred in 7 patients, 4 of whom developed jaundice and died of rapidly progressive hepatic coma, all 4 having hepatic metastatic disease and low serum albumin levels before azacitidine therapy).

Weiss AJ, Metter GE, Nealon TF, Keanan JP, Ramirez G, Swaiminathan A, Fletcher WS, et al. Phase II study of 5-azacytidine in solid tumors. Cancer Treat Rep 1977; 61: 55-8. PubMed PMID: 67894.

(177 patients with advanced cancer or lymphoma were treated with azacitidine [1.6 mg/kg/day] for 10 days, followed by a rest period and then infusions every 2 weeks for 8 weeks; "hepatic failure" occurred in 7% of 150 who received it by rapid intravenous infusion, but in none of 27 in whom it was given by slow infusion).

Armitage JO, Burns CP. Treatment of refractory adult acute nonlymphoblastic leukemia with subcutaneous 5-azacytidine. Cancer Treat Rep 1977; 61: 1721-3. PubMed PMID: 74285.

(Among 10 patients with refractory leukemia in a pilot study of subcutaneous azacitidine, 3 had mild elevations in bilirubin and AST which resolved promptly after each course).

Véz-Garcia E, Vogler WR, Bartolucci AA, Arkun SN. Twice weekly 5-azacytidine infusion in dissmeinated metastatic cancer: a phase II study. Cancer Treat Rep 1977; 61: 1675-7. PubMed PMID: 74283.

(Among 91 patients with metastatic cancer or refractory lymphoma treated with intravenous infusions of azacitidine, one patient had minor degrees of "hepatic dysfunction").

Bellet RE, Catalano RB, Mastrangelo MJ, Berd D. Phase II study of subcutaneously administered 5-azacytidine (NSC-102816) in patients with metastatic malignant melanoma. Med Pediatr Oncol 1978; 4: 11-5. PubMed PMID: 75498.

(Among 30 patients with metastatic melanoma treated with azacitidine [100 mg/m2/day] for 10 days, with repeated courses at 35 day intervals; side effects included nausea, vomiting, alopecia, diarrhea rash and pruritus: "there was no evidence of hepatic ... toxicity").

Peterson BA, Bloomfield CD, Gottlieb AJ, Coleman M, Greenberg MS. 5-azacitidine and zorubicin for patients with previously treated acute nonlymphocytic leukemia: a Cancer and Leukemia Group B pilot study. Cancer Treat Rep 1982; 66: 563-6. PubMed PMID: 6174230.

(Among 29 patients with refractory leukemia treated with azacitidine and zorubicin [an anthracycline similar to doxorubicin], toxicity was severe, 15 patients developed liver test abnormalities, 5 became jaundiced, and one died of suspected hepatic failure).

Sznol M, Ohnuma T, Holland JF. Hepatic toxicity of drugs used for hematologic neoplasia. Semin Liver Dis 1987; 7: 237-56. PubMed PMID: 3317861.

(Review describes azacitidine as a pyrimidine analogue with activity in acute leukemia; "there is scant evidence of azacitidine hepatotoxicity").

Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, Stone RM, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002; 20: 2429-40. PubMed PMID: 12011120.

(Among 191 patients with myelodysplasia treated with azacitidine or supportive care, response rates and survival were greater with azacitidine and the major toxicity was hematologic; no mention of ALT elevations or liver injury).

Kaminskas E, Farrell AT, Wang YC, Sridhara R, Pazdur R. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. Oncologist 2005; 10: 176-82. PubMed PMID: 15793220.

(Summary of the efficacy and safety results that led to the approval of azacitidine as therapy for myelodysplastic syndromes of all types; "liver function abnormalities occurred, for the most part, in patients with intercurrent illnesses, including hepatobiliary disorders. More severe abnormalities occurred in patients with previously diagnosed liver cirrhosis").

Vigil CE, Martin-Santos T, Garcia-Manero G. Safety and efficacy of azacitidine in myelodysplastic syndromes. Drug Des Devel Ther 2010; 4: 221-9. PubMed PMID: 20957213.

(Review of the mechanism of action, pharmacokinetics, efficacy and safety of azacitidine; mentions that caution should be used in treating patients who have hepatic dysfunction, because early studies reported liver injury and hepatic coma in patients with liver metastases).

Santini V, Fenaux P, Mufti GJ, Hellströindberg E, Silverman LR, List A, Gore SD, et al. Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine*. Eur J Haematol 2010; 85: 130-8. PubMed PMID: 20394651.

(Review of side effects of azacitidine and their management; the most common adverse events are bone marrow suppression, gastrointestinal complaints and injection site reactions; no mention of ALT elevations or liver toxicity).

Garcia-Manero G, Gore SD, Cogle C, Ward R, Shi T, Macbeth KJ, Laille E, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. J Clin Oncol 2011; 29: 2521-7. PubMed PMID: 21576646.

(Phase 1 study of oral doses of azacitidine after an initial subcutaneous course in 41 patients with CML; oral doses were escalated to tolerance; dose limiting side effects included nausea and diarrhea; no mention of ALT abnormalities or liver injury).

Breccia M, Loglisci G, Salaroli A, Serrao A, Petrucci L, Mancini M, Alimena G. 5-azacitidine efficacy and safety in patients aged >65 years with myelodysplastic syndromes outside clinical trials. Leuk Lymphoma 2012; 53: 1558-60. PubMed PMID: 22280532.

(Open label study of azacitidine in 38 elderly patients with myelodysplasia; common side effects were cytopenia, gastrointestinal upset and rash; no mention of ALT elevations or liver toxicity).

Pollyea DA, Kohrt HE, Gallegos L, Figueroa ME, Abdel-Wahab O, Zhang B, Bhattacharya S, et al. Safety, efficacy and biological predictors of response to sequential azacitidine and lenalidomide for elderly patients with acute myeloid leukemia. Leukemia 2012; 26: 893-901. PubMed PMID: 22033493.

(Open label study of azacitidine followed by lenalidomide in 18 elderly patients with acute myeloid leukemia; side effects included bone marrow suppression, neutropenic fever, fatigue, nausea and vomiting; no mention of ALT elevations or hepatotoxicity).

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).

Pleyer L, Burgstaller S, Girschikofsky M, Linkesch W, Stauder R, Pfeilstocker M, Schreder M, et al. Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian Azacitidine Registry of the AGMT-Study Group. Ann Hematol 2014; 93: 1825-38. PubMed PMID: 24951123.

(Among 302 Austrian patients with acute myeloid leukemia treated with azacitidine the overall response rate was 48% and serious adverse events were common, but mostly hematologic; serum enzyme elevations were recorded in 4 patients, but there were no deaths from liver disease).

Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, Kumar R, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015; 126: 291-9. PubMed PMID: 25987659.

(Among 488 patients with acute myeloid leukemia treated with azacitidine or convensional care regimens, median overall survival was longer with azacitidine [10.4 vs 6.5 months] and adverse events were frequent in both groups; no mention of ALT elevations, hepatotoxicity or liver related deaths).

Grinblatt DL, Sekeres MA, Komrokji RS, Swern AS, Sullivan KA, Narang M. Patients with myelodysplastic syndromes treated with azacitidine in clinical practice: the AVIDA registry. Leuk Lymphoma 2015; 56: 887-95. PubMed PMID: 24956145.

(Among 421 patients with myelodysplastic syndromes treated with azacitidine ia enrolled in US registry and followed for an average of 8 months, adverse events were mostly cytopenias; no mention of ALT elevations or hepatotoxicity and no discontinuations for liver related adverse events).

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. *(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [5.5%]* PubMed PMID: 25754159.

were attributed to antineoplastic agents, but none to azacitidine).

Scott LJ. Azacitidine: A review in myelodysplastic syndromes and acute myeloid leukaemia. Drugs 2016; 76: 889-900. PubMed PMID: 27193945.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of azacitidine; mentions that non-hematologic adverse events include diarrhea, constipation, nausea, skin rash and injection reactions; no mention of liver related adverse events).

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 Turkish patients with refractory anemia treated with azacitidine or decitabine, response rates were similar as were overall survival and adverse event rates; no mention of ALT elevations, hepatotoxicity or non-hematologic adverse events).

Pappa V, Anagnostopoulos A, Bouronikou E, Briasoulis E, Kotsianidis I, Pagoni M, Zikos P, et al. A retrospective study of azacitidine treatment in patients with intermediate-2 or high risk myelodysplastic syndromes in a real-world clinical setting in Greece. Int J Hematol 2017; 105: 184-95. PubMed PMID: 27815858.

(Among 88 Greek patients with myelodysplastic syndromes treated with azacitidine and followed in 17 hospitals, 42% had at least one serious adverse event, but most were cytopenias and none were liver related).