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Lurbinectedin

Updated: November 22, 2022.

OVERVIEW

Introduction

Lurbinectedin is an antineoplastic alkylating agent and synthetic derivative of trabectedin that is used to treat refractory, metastatic small cell lung cancer. Lurbinectedin therapy is associated with a high rate of transient serum enzyme elevations during treatment and with occasional instances of clinically apparent liver injury with jaundice.

Background

Lurbinectedin (loor" bin ek' te din) is a synthetic derivative of the natural product trabectedin that acts as an alkylating agent and is used in cancer chemotherapy. Lurbinectedin binds to the minor groove of DNA, allowing for alkylation of guanine causing double-strand DNA breaks and apoptotic cell death, particularly in the absence of viable DNA repair pathways. Lurbinectedin demonstrated cytotoxic activity against several cancer cell lines in vitro and in murine models of human small cell lung cancer (SCLC). Pilot studies and moderately sized, open label trials of lurbinectedin in patients with refractory, relapsed metastatic SCLC showed promising results with response rates of 35% overall. Lurbinectedin was given accelerated approval in 2020 as therapy of patients with metastatic SCLC after relapse following first line therapy with platinum based antineoplastic agents. Lurbinectedin is given intravenously and is available in 4 mg amounts of lyophilized powder in single use vials under the brand name Zepzelca. The typical dose is 3.2 mg/m^2 body surface area as a 60 minute infusion every 3 weeks, continued until disease progression or unacceptable toxicity. Premedication with dexamethasone and with serotonin antagonists (such as ondansetron) before each infusion is recommended. Side effects are common and include bone marrow suppression, anemia, neutropenia, thrombocytopenia, fatigue, nausea, vomiting, diarrhea, constipation, anorexia, abdominal pain, musculoskeletal pain, fever, dyspnea, cough, infections, peripheral neuropathy, and headache. Serious adverse events include severe myelosuppression, neutropenic sepsis, hepatotoxicity, and embryo-fetal toxicity.

Hepatotoxicity

Elevations in serum aminotransferase levels arise in approximately two-thirds of patients treated with lurbinectedin and elevations above 5 times the upper limit of normal occur in 4% to 5% of patients. Pretreatment with dexamethasone appears to decrease the degree and frequency of enzyme elevations. The elevations arise within 2 to 5 days of the intravenous infusion, rise to maximal levels between 5 and 9 days, and generally fall to baseline values within 2 to 3 weeks. Minor elevations in serum alkaline phosphatase and bilirubin are also common. However, clinically apparent liver injury with jaundice from lurbinectedin is uncommon. On the other hand, patients with underlying liver disease appear to be at increased risk for

septicemia and multiorgan failure as a result of chemotherapy, and monitoring of liver tests before and during lurbinectedin therapy is recommended. The severe liver injury typically mimics acute decompensation of an underlying cirrhosis with modest elevations in serum enzymes and worsening jaundice and hepatic synthetic dysfunction. Immunoallergic and autoimmune features are uncommon. Fatalities are generally due to sepsis and multiorgan failure rather than typical acute liver failure.

Likelihood score: D (possible cause of clinically apparent liver injury, generally in the setting of preexisting liver disease and use of high doses).

Mechanism of Injury

The transient serum aminotransferase elevations that occur with lurbinectedin therapy are most likely due to direct hepatotoxicity. Lurbinectedin is extensively metabolized by the hepatic cytochrome P450 system, predominantly CYP3A4, and is susceptible to drug-drug interactions. Agents that inhibit CYP3A activity may cause elevated levels of lurbinectedin and increased toxicity.

Outcome and Management

The severity of liver injury from lurbinectedin ranges from mild elevations in liver enzymes to marked aminotransferase elevations to clinically apparent liver injury with jaundice and multiorgan (including hepatic) failure. Most severe cases occur in patients with preexisting liver disease. For these reasons, patients should be monitored with routine liver tests before and during therapy, and therapy delayed until resolution of the abnormalities, or stopped if liver test abnormalities persist.

Drug Class: Antineoplastic Agents, Alkylating Agents

Other Drugs in Same Class: Trabectedin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lurbinectedin – Zepzelca®

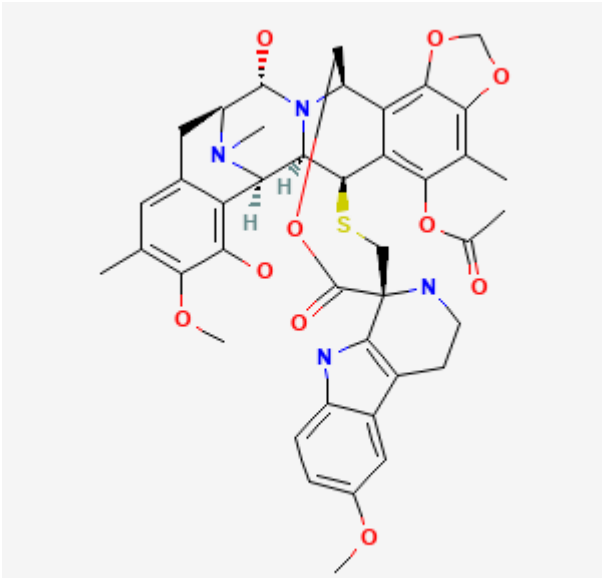
DRUG CLASS

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
Lurbinectedin	497871-47-3	C41-H44-N4-O10-S	

ANNOTATED BIBLIOGRAPHY

References updated: 22 November 2022

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 before the availability of trabectedin or lurbinectedin).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 541-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents; trabectedin is listed as causing serum enzyme elevations and rare instances of liver failure when given in high doses; lurbinectedin is not discussed).

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Trabectedin. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1194.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213702Orig1s000MultidisciplineR.pdf

(FDA web site with product labels and multidisciplinary clinical reviews of approved drug applications, mentions that 41% of the 554 lurbinectedin treated subjects had serious adverse events, resulting in drug discontinuation in 9% mostly due to myelosuppression; ALT elevations arose in 61% of participants which were above 5 times ULN in 6%, arising within 3-49 days of starting [median=8 days] and lasting 7 days on average; however, there were no cases of clinically apparent hepatotoxicity with jaundice).

van Kesteren Ch, de Vooght MMM, López-Lázaro L, Mathôt RA, Schellens JH, Jimeno JM, Beijnen JH. Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin. Anticancer Drugs. 2003;14:487–502. PubMed PMID: 12960733.

(Review of the development, chemistry, mode of action and preclinical and clinical studies of trabectedin suggests that it acts by binding to the minor groove of DNA, thereby interfering with transcription factor binding to DNA and blocking transcription).

Wahab A, Rafae A, Mushtaq K, Venkata K, Sarmad R. Lurbinectedin-induced tumor lysis syndrome in small cell neuroendocrine cancer of the cecum: a first-ever case report. Am J Case Rep. 2021;22:e932081. PubMed PMID: 34125741.

(38 year old woman with metastatic, refractory small cell neuroendocrine cancer, was started on lurbinectedin as a third-line therapy and 5 days later developed abdominal pain and acute renal failure with creatinine 4.0 mg/dL, uric acid 19.3 mg/dL, phosphate 7.6 mg/dL, ALT 49 U/L, AST 429 U/L, Alk P 599 U/L, and bilirubin 2.3 mg/dL followed by pancytopenia, septicemia, multiorgan failure and death 4 days after admission).

Markham A. Lurbinectedin: first approval. Drugs. 2020;80:1345–1353. PubMed PMID: 32816202.

(Review of the mechanism of action, history of development, clinical efficacy, and safety of lurbinectedin shortly after its accelerated approval in the US; mentions that therapy is associated with high rates of ALT and AST elevations but makes no mention of serious hepatic adverse events or clinically apparent liver injury).

Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, Peters S, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21:645–654. PubMed PMID: 32224306.

(Among 105 adults with relapsed SCLC after first-line therapy who were treated with lurbinectedin [3.2 mg/m^2 every 3 weeks], the overall response rate was 35%, and adverse events arose in most patients, 72% had ALT elevations which were above 5 times ULN in 5%, but there were no treatment related deaths and no clinically apparent drug induced liver injury).

Lurbinectedin (Zepzelca) for small-cell lung cancer. Med Lett Drugs Ther. 2022;64:e198–e199. PubMed PMID: 36384771.

(Concise review of the mechanism of action, pharmacology, clinical efficacy, safety and costs of lurbinectedin shortly after its approval for use in the US, mentions that ALT and AST elevations during therapy are common).

Aix SP, Ciuleanu TE, Navarro A, Cousin S, Bonanno L, Smit EF, Chiappori A, et al. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial. Lancet Respir Med. 2022:S2213-2600(22)00309-5. Epub ahead of print.

(Among 613 adults with advanced SCLC with relapse after platinum-based chemotherapy treated with lurbinectedin [2 mg/m^2] and doxorubicin [40 mg/m^2] every 21 days or standard chemotherapy, overall median survival was 8.6 vs 7.6 months, overall response rates were 32% vs 30%, and while adverse events arose in 98% of patients, lurbinectedin had a more favorable hematological safety than standard chemotherapy; ALT elevations and hepatotoxicity not mentioned).

Manzo A, Sforza V, Carillio G, Palumbo G, Montanino A, Sandomenico C, Costanzo R, et al. Lurbinectedin in small cell lung cancer. Front Oncol. 2022;12:932105. PubMed PMID: 36110944.

(Review of the role of lurbinectedin as a second line therapy of relapsed SCLC, a cancer with a poor prognosis and few options, lurbinectedin being the first second-line therapy approved for this indication in several decades but providing only a modest extension of survival, the major toxicities of lurbinectedin being hematologic although serum aminotransferase elevations are frequent during therapy [72% in phase 2 trials]).

Singh S, Jaigirdar AA, Mulkey F, Cheng J, Hamed SS, Li Y, Liu J. Zet al. FDA approval summary: lurbinectedin for the treatment of metastatic small cell lung cancer. Clin Cancer Res. 2021;27:2378–2382. PubMed PMID: 33288660.

(Review of the regulatory history and basis of the FDA accelerated approval of lurbinectedin in 2020 as a second-line therapy of refractory SCLC, mentions that safety was based on 554 patients treated in open label studies mentions that hepatotoxicity was observed with ALT elevations in 61% of treated participants with a median onset of 8 days and median duration of 7 days).