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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Olaparib. [Updated 2017 Jun 1].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Olaparib

Updated: June 1, 2017.

OVERVIEW

Introduction

Olaparib is a small molecule inhibitor of poly ADP-ribose polymerase and is used as an antineoplastic agent in the therapy of refractory and advanced ovarian carcinoma. Olaparib therapy is associated with a low rate of transient elevations in serum aminotransferase during therapy and has not been linked to instances of clinically apparent liver injury.

Background

Olaparib (oh lap' a rib) is a small molecule inhibitor of poly adenine diphosphate (ADP)-ribose polymerase (PARP), an enzyme involved in DNA transcription and repair. Patients with mutations of the BRCA 1 and 2 genes are at increased risk for cancer, particularly ovarian and breast cancer in women. The BRCA gene encodes DNA repair enzymes, and tumor cells with BRCA mutations are dependent upon other DNA repair pathways and thus have an increased sensitivity to inhibition of PARP. Clinical trials of olaparib in women with BRCA 1 and 2 germline mutations and advanced, refractory ovarian carcinoma have shown response rates of 30% to 40% and prolongation of progression-free survival. Olaparib is also under evaluation as therapy for advanced breast cancer and other malignant diseases associated mutations in BRCA or other DNA repair enzymes. Olaparib received approval for use in the United States in 2014 for therapy of advanced and refractory ovarian carcinoma in women with BRAC 1 and 2 mutations. Olaparib is available in 50 mg capsules under the brand name Lynparza. The recommended dose is 400 mg by mouth twice daily. Lower doses are recommended for patients with renal impairment. Common side effects include anemia, fatigue, nausea, diarrhea, dyspepsia, abdominal pain, anorexia, cough, muscle and join pain, headache and rash. Uncommon, but potentially severe side effects include pneumonitis, myelodysplastic syndrome and embryo-fetal toxicity.

Hepatotoxicity

In large clinical trials of olaparib, abnormalities in routine liver tests were uncommon with serum aminotransferase elevations occurring in 4% of patients and values above 5 times the upper limit of normal (ULN) in 1% or less. In trials of olaparib in patients with various advanced solid tumors there were no reports of hepatitis with jaundice or liver failure. Subsequent to its approval and more widescale use, there have been no published reports of clinically apparent liver injury attributed to olaparib.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of injury accounting for serum enzyme elevations during olaparib therapy is not known. Olaparib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to production of a toxic intermediate. Because it is a substrate for CYP 3A4, olaparib is susceptible to drug-drug interactions with agents that inhibit or induce hepatic CYP 3A activity.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) during olaparib therapy should lead to dose reduction or temporary cessation. There does not appear to be cross reactivity in risk for hepatic injury between olaparib and other PARP inhibitors such as rucaparib.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Other PARP Drugs: Niraparib, Rucaparib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Olaparib – Lynparza®

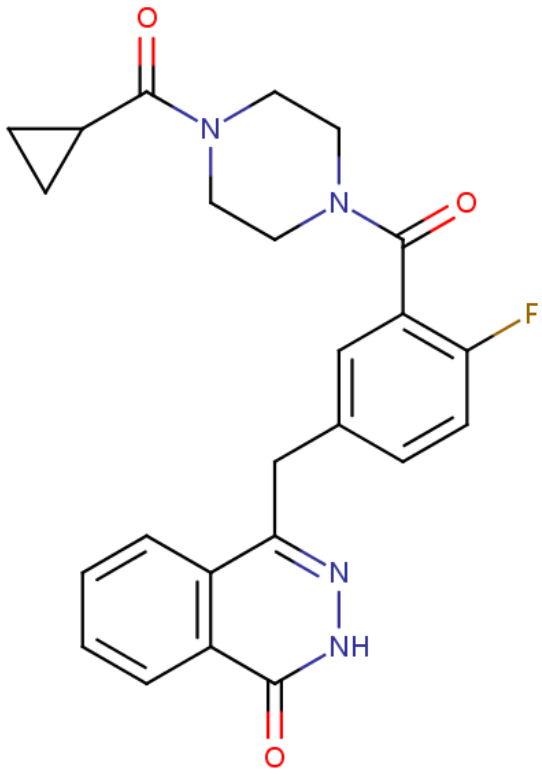
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Olaparib	763113-22-0	C24-H23-F-N4-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 01 June 2017

Abbreviations used: PARP, poly adenine diphosphate-ribose polymerase

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of protein kinase or PARP inhibitors such as olaparib).

DeLeve LD. Kinase inhibitors. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several kinase inhibitors including gefitinib, erlotinib and crizotinib, but not the PARP inhibitors such as olaparib).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, Scott C, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010; 376 (9737): 245-51. PubMed PMID: 20609468.

(Among 57 women with BRAC 1 or 2 mutations and advanced, refractory ovarian carcinoma treated with 400 vs 100 mg of olaparib twice daily, objective response rates were 33% vs 13%, while dose interruptions and reductions for adverse events were more frequent with the higher dose; no mention of ALT elevations or hepatotoxicity).

Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, Friedlander M, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010; 376 (9737): 235-44. PubMed PMID: 20609467.

(Among 54 women with BRCA 1 or 2 mutations and advanced, refractory breast cancer treated with 400 vs 100 mg of olaparib twice daily, objective response rates were 41% and 22%, while dose interruptions and reductions for adverse events were more frequent with the higher dose; no mention of ALT elevations or hepatotoxicity).

Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, Hirte H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011; 12: 852-61. PubMed PMID: 21862407.

(In an open label trial of olaparib [400 mg twice daily] in women with advanced ovarian or breast cancer, objective responses occurred in 18 of 63 [29%] women with ovarian carcinoma, but none of 26 with breast cancer; no mention of ALT elevations or hepatotoxicity).

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012; 366: 1382-92. PubMed PMID: 22452356.

(Among 265 women with advanced ovarian cancer who had a partial or complete response to platinum based chemotherapy, progression free survival was higher with olaparib than placebo [8.4 vs 4.8 months], and adverse events included nausea [68% vs 35%], fatigue [49% vs 38%] and anemia [17% vs 5%], and "there were no unexpected changes in biochemical laboratory measurements").

Kaye SB, Lubinski J, Matulonis U, Ang JE, Gourley C, Karlan BY, Amnon A, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol 2012; 30: 372-9. PubMed PMID: 22203755.

(Among 97 women with BRCA 1 or 2 mutations and advanced ovarian cancer treated with olaparib [200 or 400 mg twice daily] or doxorubicin [intravenously every 28 days], progression free survival was similar in all 3 groups and specific adverse events were not mentioned).

Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, Greninger P, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 2012; 483 (7391): 570-5. PubMed PMID: 22460902.

(Correlation of mutated cancer genes identified in cancer cell lines with their sensitivity to growth inhibition by antineoplastic agents revealed the possible role of PARP inhibition in several tumors including Ewing sarcoma).

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomized phase 2 trial. Lancet Oncol 2014; 15: 852-61. PubMed PMID: 24882434.

(Among 265 women with BRCA 1 or 2 mutations and relapsed, platinum-sensitive ovarian cancer treated with olaparib or placebo [Ledermann 2012], further follow up showed prolongation of progression free, but not overall survival with olaparib therapy and adverse events were similar to those previously reported).

Ledford H. Resurrected cancer drug faces regulators. Nature 2014; 510 (7506): 454. PubMed PMID: 24965630.

(News report on olaparib, the initial PARP inhibitor, which in early clinical trials showed little effect on survival in women with ovarian carcinoma, but on reassessment limiting analysis to cases with BRCA mutations found evidence of an effect on cancer growth, reviving interest in pursuing olaparib as therapy of selected patients with ovarian cancer).

Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, Mitchell G, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33: 244-50. PubMed PMID: 25366685.

(Among 298 patients with refractory advanced cancers and BRCA 1 or 2 mutations treated with olaparib [400 mg twice daily], the overall objective response rate was 26% and was higher in women with ovarian [31%] than breast cancer [13%]; there were no liver related serious adverse events).

Gunderson CC, Moore KN. Olaparib: an oral PARP-1 and PARP-2 inhibitor with promising activity in ovarian cancer. Future Oncol 2015; 11: 747-57. PubMed PMID: 25757679.

(Review of the development, mechanism of action, clinical efficacy and safety of olaparib in ovarian cancer; mentions that the most frequent adverse events are gastrointestinal toxicity and myelosuppression; no mention of ALT elevations or hepatotoxicity).

Bao Z, Cao C, Geng X, Tian B, Wu Y, Zhang C, Chen Z, Li W, et al. Effectiveness and safety of poly (ADP-ribose) polymerase inhibitors in cancer therapy: A systematic review and meta-analysis. Oncotarget 2016; 7: 7629-39. PubMed PMID: 26399274.

(Systematic review of the efficacy and safety of PARP inhibitors in cancer chemotherapy mentioned that in 5 placebo controlled trials, ALT elevations were no more frequent with the PARP inhibitors than in "controls", but neither were any other adverse events).

Konecny GE, Kristeleit RS. PARP inhibitors for BRCA1/2-mutated and sporadic ovarian cancer: current practice and future directions. Br J Cancer 2016; 115: 1157-73. PubMed PMID: 27736844.

(Review of role of BRCA 1 and 2 mutations in tumorigenesis and the mechanism of action of PARP inhibitors).

Ledermann JA. PARP inhibitors in ovarian cancer. Ann Oncol 2016; 27 Suppl 1: i40-i44. PubMed PMID: 27141070.

(Review of possible role of PARP inhibitors in ovarian cancer; mentions that cells with defective BRCA proteins are deficient in repair of double-stranded breaks in DNA by homologous recombination and rely on other pathways, notably PARP that detects single DNA strand breaks and activates effector proteins to initiate repair).

Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol 2016; 17: 1579-89. PubMed PMID: 27617661.

(Among 265 women with platinum-sensitive recurrent ovarian carcinoma treated with olaparib [400 mg twice daily] or placebo [Ledermann 2012], 5 year follow up showed little effect on median overall survival [29.8 vs 27.8 months]; there were no liver related severe adverse events requiring discontinuation).

Olaparib (Lynparza) for advanced ovarian cancer. Med Lett Drugs Ther 2016; 58 (1489): e32-3. PubMed PMID: 26938702.

(Concise review of the mechanism of action, clinically efficacy, safety and costs of olaparib shortly after its approval in the US; does not mention ALT elevations or hepatotoxicity).

Domchek SM, Aghajanian C, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. Gynecol Oncol 2016; 140: 199-203. PubMed PMID: 26723501.

(Among 193 women with BRCA 1 or 2 mutations and advanced refractory ovarian cancer treated with olaparib [400 mg twice daily], 34% had an objective response and side effects were common, but only 3 patients [2%] developed ALT elevations above 5 times ULN and none had clinically apparent liver injury).