Effect of Itraconazole and Rifampin on the Pharmacokinetics of Olaparib in Patients With Advanced Solid Tumors: Results of Two Phase I Open-label Studies

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ABSTRACT

Purpose: The metabolism of olaparib, a potent inhibitor of poly(ADP-ribose) polymerase (PARP) with demonstrated efficacy in patients with *BRCA*-mutated ovarian cancer, is mediated by cytochrome P450 (CYP) enzymes (predominantly CYP3A4/5). We assessed the potential of a CYP3A4 inhibitor (itraconazole) and inducer (rifampin) to alter the pharmacokinetic (PK) profile of olaparib following single oral tablet doses.

Methods: Two Phase I, open-label, non-randomized trials were conducted in patients with advanced solid tumors. In Study 7, patients received olaparib alone and co-administered with itraconazole; in Study 8, a separate group of patients received olaparib alone and co-administered with rifampin. No interaction between itraconazole and olaparib was concluded if two-sided 90% CIs for the treatment ratios of AUC and/or AUC_{0-t} and C_{max} fell within the bioequivalence range of 0.80–1.25. An interaction between rifampin and olaparib was concluded if the lower limit of the 90% CI for the treatment ratios was <0.5 (ie, $>50\%$ decrease in olaparib AUC or C_{max} in the presence of rifampin compared with olaparib alone).

Findings: In Study 7 (N = 59; 17 male, 42 female), 56 and 53 patients were evaluable for PK analysis

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following treatment with olaparib alone and olaparib plus itraconazole, respectively; in Study 8 (N = 22; 4 male, 18 female), all patients were evaluable. Co-administration of olaparib with itraconazole resulted in a statistically significant increase in the relative bioavailability of olaparib: C_{max} treatment ratio, 1.42 (90% CI, 1.33–1.52); mean AUC treatment ratio, 2.70 (90% CI, 2.44–2.97). Mean CL/F and V_z/F were reduced (8.16 vs 3.05 L/h and 192 vs 75.1 L), although mean $t_{½}$ was unchanged (15.0 vs 15.6 hours). Co-administration of olaparib with rifampin resulted in a statistically significant decrease in the relative bioavailability of olaparib: C_{max} treatment ratio, 0.29 (90% CI, 0.24–0.33); mean AUC treatment ratio, 0.13 (90% CI, 0.11–0.16). CL/F and V_z/F were increased when olaparib and rifampin were co-administered (6.36 vs 48.3 L/h and 112 vs 1076 L); however, mean $t_{½}$ was unchanged (13.0 vs 15.8 hours). Safety data for olaparib following tablet dosing were consistent with the known safety profile.

Implications: Exposure to olaparib was significantly increased when co-administered with the potent CYP3A4 inhibitor itraconazole, and significantly decreased when co-administered with the potent CYP3A4 inducer rifampin, compared with olaparib alone. Potent CYP3A4 enzyme inhibitors and inducers should be avoided during olaparib treatment.

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Key words: CYP3A4, itraconazole, olaparib, pharmacokinetic, rifampin.

INTRODUCTION

Olaparib* is a potent, oral poly(ADP-ribose) polymerase (PARP) inhibitor that blocks base-excision repair of single-strand DNA breaks (SSBs) by trapping PARP at sites of DNA damage.[1] PARP inhibitors also impair, via other mechanisms, high-fidelity repair of double-strand DNA breaks in tumor cells with deficiencies in homologous recombination repair (HRR), such as *BRCA1/2* mutations (*BRCA1*/2m).[2,3] The prevention of SSB repair as a result of PARP inhibition in tumor cells with HRR deficiencies leads to irreparable double-strand breaks being formed that result in tumor cell death by PARP-inhibitor-induced synthetic lethality.[4] PARP inhibitors can also induce lethality in tumor cells that have deficiencies in DNA damage repair mechanisms other than HRR deficiencies.

On 19 December, 2014, olaparib (capsule formulation) became the first PARP inhibitor approved for treatment when the United States Food and Drug Administration (FDA) granted accelerated approval of olaparib for the monotherapy treatment of patients with relapsed germline *BRCA* mutation (g*BRCAm*) ovarian cancer who have received three or more lines of chemotherapy.[5] In the same week, the European Medicines Agency (EMA) granted approval of olaparib as monotherapy maintenance treatment of adult patients with platinum-sensitive, relapsed *BRCA*m (germline and/or somatic) ovarian cancer who are in complete or partial response to platinum-based chemotherapy based on Study 19 (D0810C00019; NCT00753545) data.[6] In patients with platinum-sensitive, recurrent serous ovarian cancer, maintenance monotherapy with a capsule formulation of olaparib 400 mg twice daily (bid) significantly prolonged progression-free survival (PFS) versus placebo.[7] A prespecified retrospective analysis of this patient population showed that patients with a *BRCA*m receive greater treatment benefit.[8] In Study 42 (D0810C00042; NCT01078662), which involved patients with a germline *BRCA1/2*m and solid tumors refractory to standard therapy, treatment with a capsule formulation of olaparib 400 mg bid prolonged tumor responses across a spectrum of malignancies, including ovarian, breast, pancreatic, and prostate cancers.[9] To receive the recommended 400 mg bid dose of olaparib, patients are required to take 16 × 50 mg large capsules per day and, consequently, patient compliance may be compromised. A tablet formulation has therefore been developed to deliver a therapeutic dose in fewer and smaller units. A recommended tablet dose of 300 mg bid has been determined in a Phase I trial (Study 24, D0810C00024; NCT00777582) for administration in Phase III studies.[10]

In vitro data have shown that the metabolism of olaparib is mediated by cytochrome P450 (CYP) enzymes (predominantly CYP3A4/5); co-administration with potent inhibitors or inducers of CYP3A4 would therefore be

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