GENETICS

PARP inhibitor has antitumor activity

The tumor suppressor proteins BRCA1 and BRCA2 have important roles in the DNA repair pathway. Tumors in patients with a *BRCA1* or *BRCA2* mutation (such as breast, ovarian and prostate cancer) can be inhibited by poly(ADP-ribose) polymerase (PARP) inhibitors owing to the key role of PARP in repairing DNA single-strand breaks. Fong and colleagues conducted an evaluation of the novel PARP inhibitor, olaparib, in humans.

This phase I trial was designed to analyze the safety, adverse-effect profile, maximum tolerated dose and pharmacokinetic and pharmacodynamic properties of olaparib in a population of patients with a *BRCA1* or *BRCA2* mutation. Eligibility criteria included age 18 years or above, refractory disease, an Eastern Cooperative Oncology Group performance status of 2 or less, and sufficient bone marrow, hepatic and renal function. The authors hypothesized that patients with a *BRCA1* or *BRCA2* mutation would demonstrate an objective antitumor response to olaparib.

The initial dose and schedule of olaparib was 10 mg once daily for 2 of every 3 weeks, and this was subsequently increased to 600 mg twice daily continuously in 4-week cycles. Safety evaluations were carried out at baseline and at weekly visits.

A total of 60 patients were included, 22 of these were *BRCA* mutation carriers. Reversible dose-limiting toxic effects were observed in three patients, one

of these patients received 400 mg of olaparib twice daily and the other two patients received 600 mg twice daily. The investigators therefore established the maximum tolerated dose of olaparib as 400 mg twice-daily. The majority of adverse effects were grade 1 or 2, including nausea, vomiting, fatigue and anorexia. *BRCA* mutation carriers had no obvious increase in adverse effects. Pharmacodynamic analysis revealed that olaparib is rapidly absorbed and eliminated. Mutation carriers who had received multiple treatment regimens were the only patients to have objective antitumor activity. Patients treated with 60 mg or more of olaparib showed more than 90% inhibition of PARP compared with baseline.

The results of this phase I trial show that olaparib inhibits PARP, has an acceptable adverse-effect profile and has antitumor activity in tumors associated with *BRCA1* or *BRCA2* mutations. The authors conclude that the traditional process of clinical development needs to be altered for some anticancer drugs and “due consideration must now be given to developing rationally designed, molecularly targeted therapies for patients whose tumors have the same molecular defect but different origins”.

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Original article Fong, P. C. *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N. Engl. J. Med* **361**, 123–134 (2009).