Revolutionary therapy slows tumor growth in advanced breast cancer

July 5 2010

The new drug olaparib has antitumour activity in carriers of the BRCA1 or BRCA2 gene mutations who have advanced ovarian or breast cancer, according to the findings of two proof-of-concept trials. Together with previous findings, these trials suggest that therapy for ovarian, breast, and possibly other cancers can be targeted on the basis of shared genetic defects, rather than organ of origin, conclude the Articles published online in the *Lancet*.

About 10% of women with ovarian cancer and up to 5% of women with breast cancer carry a mutation in the genes BRCA1 or BRCA2, which confers a high risk of development of breast and ovarian cancer. BRCA1 and BRCA2 are tumour-suppressor genes - key components of the homologous recombination repair pathway that repairs breaks in both strands of DNA. Up until now, knowledge of a BRCA mutation has not affected the selection of treatment for ovarian or breast cancer. In cancer models with BRCA1 or BRCA2 mutation, blockade of poly(ADP-ribose) polymerase (PARP), which is important to repair single-strand DNA breaks, synthetically kills the mutated cancer cells. The combination of two repair defects induces killing of the cells. These findings indicate that olaparib, a new, oral PARP inhibitor that kills BRCA-deficient cells, might be useful as a cancer treatment in patients with these mutations.

An international team led by Andrew Tutt (Breakthrough Breast Cancer Research Unit, King's College London School of Medicine, London, UK), conducted two proof-of-concept trials to assess the efficacy and

safety of olaparib for treatment of advanced ovarian or breast cancer in patients with BRCA1 or BRCA2 mutations. In the first multicentre, phase 2 study, the team enrolled two sequential cohorts of adult women with confirmed genetic BRCA1 or BRCA2 mutations, and recurrent, measurable ovarian cancer. In the second multicentre, phase-2 study, adult women with confirmed BRCA1 or BRCA2 mutations and recurrent, advanced breast cancer were also assigned to two sequential cohorts. The first cohort in each study was given continuous oral olaparib at the maximum tolerated dose of 400 mg twice daily, and the second cohort was given continuous oral olaparib at 100 mg twice daily. The primary efficacy endpoint for both trials was objective response rate (ORR) and funding was from AstraZeneca.

Findings indicated better treatment response with the higher dose of olaparib compared with lower dose in both trials. In the ovarian cancer study, patients had already received a median of three previous chemotherapy regimens. ORR was 33% of 33 patients in the cohort assigned to olaparib 400 mg twice daily, and 13% of 24 in the cohort assigned to 100 mg twice daily. In the breast cancer study, patients had been given a median of three previous chemotherapy regimens. ORR was 41% of 27 patients in the cohort assigned to 400 mg twice daily, and six 22% of 27 in the cohort assigned to 100 mg twice daily. In both studies, olaparib was generally well tolerated, with most adverse events being low grade. Findings from both phase 2 studies provide positive proof of concept of the efficacy and tolerability of genetically targeted treatment with olaparib in BRCA-mutated advanced ovarian or breast cancer, note the authors.

In the report on ovarian cancer, first author M William Audeh (Samuel Oschin Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA) and colleagues explain: "The results of this phase 2 study show that the oral PARP inhibitor olaparib, given as monotherapy at a dose of 400 mg twice daily, has antitumour activity in heavily pretreated carriers

of the BRCA1 or BRCA2 mutation who have recurrent ovarian cancer. Olaparib 100 mg twice daily also had clinical activity in this population, but this dose seems to be less efficacious than the 400 mg twice daily dose. However, the allocation of patients to these doses was not randomised and the olaparib 100 mg cohort had poorer prognostic features than did the 400 mg cohort."

The authors conclude that these findings support the hypothesis that BRCA-mutated tumours are susceptible to the synthetic killing induced by olaparib. "These data also support the identification of BRCA1 or BRCA2 mutations as a predictive biomarker for responsiveness to PARP inhibition," they note. Identification of other defects in the repair pathway that involves BRCA1 and BRCA2 "could predict similar responsiveness to PARP inhibition in a broad, genetically defined group of malignant diseases", they write.

In the report on breast cancer, first author Tutt and colleagues write: "The results of this phase 2 study show that the oral PARP inhibitor olaparib at 400 mg twice daily was active even in women with BRCA1 or BRCA2 mutations and advanced breast cancer that was resistant to conventional chemotherapy". These findings provide proof-of-concept for targeting the DNA repair pathway associated with BRCA1 or BRCA2 in patients with breast cancer, they explain.

The authors conclude that "the results of this study have shown that knowledge of cancer predisposition gene function can be translated from the laboratory to successfully test clinical treatment hypotheses for this rare group of women with hereditary breast cancer." The results of the study support further investigation of this approach that combines inhibition of a DNA repair target (such as with olaparib) with an inherent loss of function of specialised DNA repair (such as that due to BRCA mutations), the authors note. "Whether this approach might also show efficacy in a broader group of sporadic breast and ovarian cancers

that might have inactivation of the homologous recombination repair pathway will be tested in future trials," the team explain.

Provided by Lancet