Olaparib shows promise in treating ovarian cancer, even without BRCA mutations

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The PARP inhibitor, olaparib, that has shown promise in women with an inherited mutation in their BRCA1 or BRCA2 gene (accounting for about 5-10% of breast and ovarian cancer cases), has, for the first time, been shown to reduce the size of tumours in a much wider group of ovarian cancer patients without these BRCA gene mutations. The findings, published Online First in *The Lancet Oncology*, highlight the potential of olaparib to treat patients with more common sporadic (non-hereditary) tumours and could offer a new treatment option for one of the most deadly cancers in women.

"Olaparib represents a promising therapeutic option for patients with this aggressive malignant disease for whom treatment options are limited to toxic chemotherapies", explains lead author Karen Gelmon from the BC Cancer Agency, Vancouver, Canada.

Olaparib works by blocking the activity of a protein called Poly (ADP ribose) polymerase (PARP). Both PARP and BRCA proteins are involved in DNA repair. Inhibiting PARP in a tumour that already lacks a BRCA gene prevents cancer cells from repairing their DNA (enhancing the effectiveness of DNA-damaging chemotherapy) and causes them to die-a process known as synthetic lethality.*

Until now, whether olaparib could also be effective in a broader group of sporadic breast and ovarian cancers that might share similar DNA repair deficiencies, such as triple-negative breast cancer and high-grade serous ovarian cancer, was not known.

The phase 2 trial was designed to evaluate the drug's effectiveness in the treatment of breast and ovarian cancer without BRCA gene mutations. Between July, 2008, and September, 2009, 92 patients (65 with ovarian cancer and 26 breast cancer) were given olaparib 400 mg twice daily for 4 weeks, and classified according to their BRCA1 and BRCA2 mutation status.

Among women with ovarian cancer, 41% with BRCA mutations showed a substantial shrinkage in the size of their tumours compared with 24% of patients without mutations. None of the patients with breast cancer had an objective response.

Olaparib was generally well tolerated and most side effects were mild, including fatigue, nausea, vomiting, and decreased appetite. The authors conclude: "New treatments targeting DNA repair mechanisms seem to provide new hope for treatment of ovarian cancer."

In a Comment, Melinda Telli from Stanford University School of Medicine, California, USA discusses the potential of this new class of genetically-targeted drugs and remarks: "For the first time, activity of a PARP inhibitor as monotherapy in women with advanced high-grade serous ovarian cancer who do not have a germline BRCA1 or BRCA2 mutation [has been shown]. This finding not only suggests new therapeutic possibilities for women with this aggressive type of ovarian cancer, but also importantly confirms the hypothesis that subpopulations of patients with common sporadic tumours can be targeted effectively with PARP inhibitor therapy."

More information: Paper online: www.thelancet.com/journals/lan ... (11)70214-5/abstract

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