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Understanding of the mechanisms of drug resistance to dual-agent chemotherapy in ovarian cancer

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More than half of all patients with ovarian cancer experience recurrent disease and will eventually fail to respond to chemotherapy. The failure of chemotherapy is usually due to the development of resistance to the two main classes of chemotherapy agents used to fight it – platinating agents and taxanes. Now, a study reported in the open-access *Journal of Ovarian Research* provides novel information that further adds to clinicians' understanding of the mechanisms involved in the development of resistance to dual-agent chemotherapy.

It was not known whether mechanisms of resistance to dual-agent chemotherapy are a combination of single-agent resistance responses or if novel mechanisms arise as a result of combined platinating agent/taxane therapy. Carita Lanner and her team, from Sudbury, Ontario, in Canada, provide evidence to suggest that the latter is true: novel and different changes occur to cause resistance to the dual combination of agents.

Ovarian cancer is the most lethal gynecological cancer, with a 5-year mortality rate of over 50%. A significant contributing factor to the high mortality rate is the development of resistance to chemotherapy regimens. The differences in mode of action and mechanisms of resistance for platinating agents and taxanes are taken advantage of in dual-agent chemotherapy of advanced cancer. Used together, they achieve increased efficacy and progression-free survival in patients.

However, combined resistance to both agents may occur, and is more difficult to overcome than single-agent resistance.

Lanner and colleagues set out to investigate if the development of dual agent resistance invokes different mechanisms or is a combination of the mechanisms of resistance that arise upon exposure to single agents. To do this, they developed a set of isogenic ovarian cancer cell lines resistant to either (1) the platinating agent carboplatin, (2) the taxane docetaxel, or (3) a combination of carboplatin and docetaxel. They analyzed changes in gene expression associated with the specified drug resistance in each cell line using microarray analysis.

The team compared the three resistant cell lines to identify shared and different changes in gene expression amongst all three treatments. The analysis showed that the establishment of carboplatin and docetaxel resistance did not share many changes in gene expression. Most significantly, dual-agent resistance appeared to develop from mostly unique changes in gene expression, different from both single carboplatin and docetaxel resistance in the set of isogenic cell lines studied.

Lead author Carita Lanner commented, "These results demonstrate that combined drug resistance is NOT just a combination of changes present in single agent-resistant cells but contains different and new changes. The dual carboplatin-docetaxel resistant cell line will facilitate further investigation into mechanisms underlying the development of dual drug resistance in ovarian cancer."

More information: Distinct genetic alterations occur in ovarian tumor cells selected for combined resistance to carboplatin and docetaxel Stephen R Armstrong, Rashmi Narendrula, Baoqing Guo, Amadeo M Parissenti, Katherine L McCallum, Stephanie Cull and Carita Lanner, *Journal of Ovarian Research* (in press)