Researchers map the way to personalised treatment for ovarian cancer

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mis-spellings in a single letter of genetic code – that drive the onset and growth of cancer cells can be detected successfully in advanced ovarian cancer using a technique called OncoMap. The finding opens the way for personalised medicine in which every patient could have their tumour screened, specific mutations identified, and the appropriate drug chosen to target the mutation and halt the growth of their cancer.

Using mass spectrometry for identifying the genetic make-up of cancer cells, OncoMap can determine the point mutations in a large panel of over 100 known cancer-causing genes (oncogenes) in tumours. In the work to be presented today (Wednesday) at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Berlin, researchers will describe how they used OncoMap to identify mutations in oncogenes in tumour samples from women with advanced high-grade serous ovarian cancer. Earlier in the year 76 mutations in 26 different genes had been found but, since then, further work in more tumour samples has found more.

Dr Ursula Matulonis, director/program leader in medical gynaecologic oncology at the Dana Farber Cancer Institute in Boston (Massachusetts, USA) and Associate Professor of Medicine at Harvard Medical School, will tell the meeting: "Epithelial ovarian cancer is the most lethal of all the gynaecologic malignancies, and new treatments are needed for both newly diagnosed patients as well as patients with recurrent cancer. The success of conventional chemotherapy has reached a plateau, and new means of characterising ovarian cancer so that treatment can be

personalised are needed.

"We know that many human cancers have point mutations in certain oncogenes, and that these mutations can cause cancer cells to have a dependence on just one overactive gene or signalling pathway for the cancer cell's growth and survival – a phenomenon known as 'oncogene addiction'. If the mutation that causes the oncogene addiction can be inhibited, then it seems that this often halts the cancer process. Examples of mutations that are successfully inhibited by targeted drugs are HER2 (for which trastuzumab is used in breast cancer), EGFR (erlotinib in lung cancer) and c-kit (imatinib in chronic myeloid leukaemia). So if we know the status of specific genes in a tumour, then this enables us to choose specific treatments that are likely to work successfully against the cancer."

Dr Matulonis and her colleagues used OncoMap to investigate the mutation status of high-grade serous ovarian tumours that were known not to be caused by inherited mutations in the BRCA 1/2 genes. They found mutations previously identified to be involved in ovarian cancer: KRAS, BRAF, CTNNB1 and PIK3CA. The KRAS and PIK3CA mutations were the most common, while BRAF was more rare. The researchers also identified a low frequency of mutations in many other different oncogenes.

"This study shows that it's feasible to use OncoMap to identify whether a patient's tumour has a mutation in an oncogene for which a known drug is available to target that specific gene, so as to enable us to place her on a clinical study of that drug; for instance, XL147 or GDC0941 are inhibitors for the P13kinase mutation that are in clinical trials at present," said Dr Matulonis. "In addition, someone's cancer could harbour a mutation (such as ALK) that is not known to be associated with ovarian cancer or has not yet been studied in ovarian cancer – these patients could be matched with a drug that inhibits that protein too. As

new drugs get developed, this information would be used to match future drugs with patients and their cancers."

The researchers hope that OncoMap will become a clinical test for all cancer patients at the Dana Farber Cancer Institute before long, so that the genetic information obtained can be used to choose the best treatment for them.

"At present, only a few targeted therapies are being used for newly diagnosed ovarian cancer and most are being used to treat recurrent ovarian cancer, but this will change eventually. I have already referred several of our patients who are either newly diagnosed or have recurrent cancer and who have mutations (one with KRAS and one with PIK3CA) to our phase I programme for drugs studies specific to these mutations," said Dr Matulonis.

She believes that OncoMap and other similar analytical tools will become mainstream practice in all cancer clinics before long. Tools for detecting genes with the incorrect numbers of copies or abnormal expression will also help doctors to choose the best treatment for individual patients.

"For ovarian cancer, understanding mutational analysis is one piece of the genetic puzzle. Our group will also start looking for chromosomal and gene amplifications and deletions in patients' tumours, which we know are important for ovarian cancer."

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