Blood tests predict which prostate cancer patients are resistant to chemotherapy drug

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Regular blood tests before and during chemotherapy for prostate cancer can detect whether or not a patient is resistant or developing resistance to treatment with docetaxel, according to research presented at the NCRI

Festival.

The findings could enable doctors to detect early on, without invasive procedures, if a treatment is working and switch to alternatives such as abiraterone or cabazitaxel if it is not.

Men with prostate cancer that has started to spread to other parts of the body (metastasised) and does not respond to therapy to lower levels of the hormone androgen, are often treated with docetaxel, a chemotherapy that can significantly improve survival. However, some patients are resistant or acquire resistance to docetaxel.

Ms Caitlin Davies, a Ph.D. research student at Barts Cancer Institute, Queen Mary University of London, UK, and colleagues investigated if it would be possible to identify docetaxel resistance and predict survival from the number and types of cancer cells that have detached from the tumour and entered the bloodstream; these are called circulating cancer cells or CTCs.

They took blood samples from 56 patients with advanced prostate cancer who were being treated at St Bartholomew's Hospital, London. The samples were taken before they started docetaxel treatment, after their first dose of chemotherapy, before their fifth dose, and once they'd finished all doses—a period of approximately six to eight months. Depending on the availability of the patients, the number of samples per patient ranged from two to four. A total of 205 samples were available for analysis.

"Our ability to collect and analyse CTCs before, during and after treatment meant that we could monitor changes in CTCs in response to treatment," said Ms Davies.

The researchers used a blood filtration system called Parsortix to

identify CTCs based on their larger size compared to other components in the blood, such as white blood cells. It also captures different subtypes of CTCs.

"We then looked for patterns in the data from men who responded or did not, or whose disease progressed sooner than others after treatment. Using these patterns, we can apply them to future patients with the goal to predict whether they will respond to therapy and pre-emptively decide on the best course of action that will have maximal benefit. For instance, an increase in CTC numbers may indicate a lack of response to treatment. Furthermore, by monitoring the appearance of potentially drug-resistant CTCs, we can change treatment tactics early on and in a patient-personalised and timely manner."

The researchers found that men were less likely to respond to docetaxel, their disease was more likely to recur or progress within three months, and they were more likely to die within 18 months if more than six CTCs per 7.5mL of blood were detected before their first docetaxel dose. This compared to progression-free survival of 17 months and an overall survival time of three years for men with fewer than six CTCs detected per 7.5mL of blood.

Among the several subtypes of CTCs, the researchers found that having more than one 'classic' type of CTC (epithelial, cytokeratin positive cells or E-CTCs) before docetaxel treatment predicted that the disease would progress within two months following treatment, instead of more than a year later. It also predicted survival: nine months versus 32 months for those without E-CTCs

High numbers of CTCs towards the end of treatment predicted a shorter time to disease progression and death. The disease was eight times more likely to progress within six months in patients who showed an increase in another type of CTC (CTCs without epithelial features) than those

who did not have an increase.

"This insight into how CTC dynamics lead to reduced progression-free and survival times is vital for clinicians. It will enable them to make early changes of treatment from docetaxel to an alternative, which may significantly improve patients' chances of long-term survival," said Ms Davies.

The researchers also discovered that a protein encoded by a gene called *KLK2* was significantly better at predicting time to disease progression and death than the current gold standard protein, prostate-specific antigen (PSA), which is encoded by the *KLK3* gene.

"There were high levels of the *KLK2* gene expression in patients who did not respond to docetaxel, and this elevated expression was also associated with a shorter time to disease progression and death. These are important findings as they highlight *KLK2* as a possible alternative and better biomarker for prostate cancer prognosis," said Ms Davies. "Analysis of CTC gene expression and detection of genes associated with resistance to docetaxel may aid the development of a new generation of therapies."

This way of testing for CTCs in blood samples is known as liquid biopsy. "It is minimally invasive, painless and easily repeatable, so patients can avoid undergoing painful tissue biopsies. It takes a matter of minutes for the patient, and we can get results within two to three days, whereas a tissue biopsy can take up to ten days. Liquid biopsies are very cost-effective compared to tissue biopsy, CT scans or MRI," said Ms Davies.

She concluded: "Although these results are highly promising, they require further validation in a larger group of patients, perhaps in a clinical trial."

The researchers are continuing to research and validate the use of CTCs as biomarkers for prostate cancer. They are investigating a number of genes in CTCs that may be involved in resistance to docetaxel in order to understand the mechanisms and identify new targets for anti-cancer drugs.

Hashim Ahmed, Chair of the NCRI Prostate Group and Professor of Urology at Imperial College London, UK, who was not involved in the research, said: "These are promising results and have the potential to change clinical practice, if they are confirmed by further research. Assessing the responsiveness of an individual patient's tumour to docetaxel treatment by means of blood tests will enable clinicians to personalise cancer treatment more easily and effectively, without the patient having to undergo invasive procedures such as tissue biopsies. It could also help to avoid patients undergoing unpleasant systemic treatments that are going to be unsuccessful."

Provided by National Cancer Research Institute

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