How highs and lows in testosterone levels 'shock' prostate cancer cells to death

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Munich, Germany: A strategy of alternately flooding and starving the body of testosterone is producing good results in patients who have metastatic prostate cancer that is resistant to treatment by chemical or surgical castration, according to new findings.

In a presentation at the 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Munich, Germany, today (Thursday), researchers reported that results from 47 men who have completed at least three cycles of bipolar androgen therapy (BAT) showed that the strategy was safe and effective. Prostate specific antigen (PSA) levels fell in the majority of the men, tumours shrank in some men, in several the disease did not progress and this included some whose disease continued to be stable for more than a year. One man appears to have been "cured", in that his PSA levels dropped to zero after three months and have remained so for 22 cycles of treatment, with no trace of the disease remaining. The researchers are planning to treat a group of 60 men in total.

Sam Denmeade MD, professor of oncology at Johns Hopkins University School of Medicine (Baltimore, USA) told the Symposium: "We think the results are unexpected and exciting. We are still in the early stages of figuring out how this works and how to incorporate it into the treatment paradigm for prostate cancer."

Traditionally, treatments for prostate cancer have involved lowering the levels of the male hormone (or androgen) testosterone using drugs called

luteinising hormone-releasing hormone (LHRH) agonists, as it was thought that androgens stimulate the cancer cells to grow. However, Prof Denmeade says there is no evidence that testosterone promotes cancer.

"Indeed, earlier research in prostate cancer cell lines has shown that treatment with high doses of testosterone could inhibit growth and kill cancer cells. The exact mechanism is not known and there may be many things happening since the androgen receptor is the key signalling pathway in prostate cancer," he said. "In our lab we have observed that testosterone interferes with part of the cell division process in cancer cells called DNA licensing; it also seems to cause prostate cancer cells to make breaks in their DNA. So too much testosterone can cause cancer cells to die. It can also induce something we call senescence, which means the cancer cells become like old men who sit around and tell stories but don't make much trouble."

In an ongoing study called RESTORE, 47 men with castration resistant prostate cancer that had started to spread to other parts of the body (metastasise), who showed no symptoms but whose disease had become resistant to treatment with either abiraterone (17 patients) or enzalutamide (30 patients) receive a high dose of testosterone (400 mg), injected into the muscle every 28 days. At the same time the men continued on their LHRH agonist therapy to clamp down on testosterone produced naturally by the testicles. The men also stopped taking abiraterone or enzalutamide. These two anti-cancer therapies work by inhibiting androgen receptor signalling.

"Our goal is to shock the cancer cells by exposing them rapidly to very high followed by very low levels of testosterone in the blood," explained Prof Denmeade. These alternating extremes in testosterone levels are why the researchers call the therapy "bipolar".

Men with declining PSA levels or stable disease continued with BAT

after three cycles, and if their disease started to progress they were treated again with abiraterone or enzalutamide.

The study has completed enrolment of the required 30 men in the first arm of the study who were treated with testosterone after their disease became resistant to enzalutamide and started to progress. Presenting results from this group, Prof Denmeade said: "Thus far we have observed dramatic PSA response in a subset of men; PSA levels declined in about 40% of men and in about 30% of men levels fell by more than 50%. Some men also have objective responses with a decrease in the size of measurable disease, mostly in lymph nodes. Many of the men have stable disease that has not progressed for more than 12 months. I think we may have cured one man whose PSA dropped to zero after three months and has remained so now for 22 cycles. His disease has all disappeared."

So far, 17 of the 30 men in the second arm of the study whose disease had started to progress again after treatment with abiraterone have received testosterone. Prof Denmeade said: "PSA responses were also observed in this group, but full results will not be presented until all 30 men have been enrolled over the next year."

All men in the study were tested for circulating tumour cells in their blood and six of them were found to have a protein called androgen-receptor splice variant (AR-V7), which may be associated with resistance to treatment with enzalutamide. After BAT treatment, AR-V7 disappeared from the blood of all six men, and two of the men had declines in PSA levels of 50% and over.

So far, BAT has been well-tolerated by patients with no dose-limiting toxicities. One patient had an increase in pain and one had a problem with retention of urine. "The benefits of the treatment are particularly evident in men who have had no sexual function for many years due to

impotence caused by hormone deprivation. These men are quite happy with the new treatment. Other positives include increase in muscle strength, increased energy and decreased fatigue. This does not occur in every man and we are not sure exactly why."

More research still needs to be conducted on BAT. Prof Denmeade said: "We caution that this is still experimental. In particular, this therapy should only be given to men who are asymptomatic. Testosterone treatment can definitely worsen pain in men with prostate cancer who have pain from their disease."

A multi-centre randomised trial in the USA called TRANSFORMER is testing BAT versus enzalutamide in men with metastatic castrate-resistant prostate cancer whose disease had progressed after being treated with abiraterone. So far it has recruited 111 men with a target of 180. "If we find testosterone is superior then we would hope to move on to larger trials. Our problem is this is not a drug that is owned by a pharmaceutical company; it is generic testosterone. So moving forward is going to be difficult due to issues with finding funds to run a bigger trial," concluded Prof Denmeade.

Chair of the scientific committee for the Symposium, Professor Jean Charles Soria from the Institut Gustave Roussy (France), commented: "The use of testosterone in men with castration-resistant prostate cancer is an intriguing concept that was previously advocated some years ago, but this is the first time we have clinical data in patients whose disease has progressed after treatment with abiraterone or enzalutamide."

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