New targeted therapy for advanced prostate cancer shows anti-tumor activity in clinical trials

November 7 2012

Few available treatment options exist once prostate cancer has spread to other parts of the body and has failed to respond to therapies that involve blocking the male hormone androgen. Patients with advanced, hormone-refractory prostate cancer usually die from the disease after 12 to 18 months, so new therapies are desperately needed.

At the 24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland, today (Thursday), researchers will report that a new drug that specifically targets a protein found on the surface of prostate cancer cells has performed well in a phase I clinical trial, and a phase II trial has started. The drug reduced levels of circulating tumour cells (CTC) and levels of prostate specific antigen (PSA), a marker for tumour activity, in patients who had already failed previous chemotherapy and hormone treatments.

The drug is made up of a monoclonal antibody, which targets a protein called prostate specific membrane antigen (PSMA), linked to a cancer cell-killing drug called monomethyl auristatin E (MMAE), which disrupts tubulins – the tiny molecules inside a cell that are essential for cell division. The PSMA antibody drug conjugate (PSMA ADC) binds to the PSMA on the surface of the prostate cancer cell and is absorbed into the cell where the MMAE is released, causing cell cycle arrest and cell death.

Professor Daniel Petrylak, who was Professor of Medicine at Columbia University Medical Center (USA) when the phase I trial started and who is now Director of the Prostate Cancer Program/Genitourinary Cancer Program and co-director of the Signal Transduction Program at Yale University Medical Centre (USA), said: "By conjugating the antibody with a chemotherapeutic agent, we hoped that this would lead to more targeted therapy, which would have fewer toxic side-effects and would be more effective against the cancer."

Prof Petrylak and his colleagues from other US cancer centres recruited 50 patients to the phase I clinical trial. The patients had the most advanced form of prostate cancer, which had spread to the bone and other organs; they had failed hormone therapy and had received up to two previous chemotherapies. The researchers treated them with doses of PSMA ADC at levels ranging from 0.4 to 2.8 mg/kg, by intravenous infusion, over a period of three weeks per cycle, and for up to four treatment cycles.

The researchers detected anti-tumour activity among the patients who were treated at the higher doses. About half of the patients who received doses of 1.8 mg/kg or more showed either a 50% or more reduction in PSA levels, or a fall in CTC in the blood to less than five cells per 7.5 ml of blood, or both.

The drug was generally well tolerated by patients, although levels of white blood cells were significantly reduced (neutropenia) at the highest dose of 2.8 mg/kg and one patient died. The researchers say the cause of the death is unclear.

Prof Petrylak said: "These results show that PSMA ADC has anti-tumour activity in patients who have failed up to two prior chemotherapies and hormone therapy. We have initiated a phase II trial of up to 75 patients in which the recommended dose will be 2.5 mg/kg.

This new trial will evaluate responses in PSA and CTC; it will evaluate control of metastases in bone, internal organs and lymph nodes; and it will look at the effect on pain. Safety also will be assessed.

"The fact that this new targeted therapy is active against the most advanced forms of prostate cancer is encouraging, as few or no therapeutic options are available at present."

Professor Stefan Sleijfer, the scientific chair of the EORTC-NCI-AACR Symposium, from Erasmus University Medical Centre (The Netherlands), commented: "The approach tested here represents a novel way to treat prostate cancer. The anti-tumour effects already seen at such an early phase of clinical testing, such as a fall in circulating tumour cells , render this drug a promising compound for prostate cancer."

More information: Abstract no: 244. Proffered papers, plenary session 6, 15.00 hrs, Thursday 8 November.

Provided by ECCO-the European CanCer Organisation