New bone-targeting drug delays onset of metastases in hormone-resistant prostate cancer patients

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Stockholm, Sweden: Inhibiting a protein involved in bone metabolism can delay the onset of the bone metastases which are common in men with a particular form of prostate cancer, a researcher will tell the 2011 European Multidisciplinary Cancer Congress today (Sunday).

Professor Stéphane Oudard, Head of the Oncology Department at the Georges Pompidou Hospital, Paris, France, says that his team's research on the effects of the monoclonal antibody denosumab (XGEVA TM) is the first large-scale clinical trial to show such an effect.

Up to 90% of men with prostate cancer that is resistant to hormone treatment will have their primary tumour metastasise to bone. The onset of such metastases means that the cancer is entering a chronic and, thereafter, a terminal phase, and this has major physical and psychological consequences for the patient.

"Being able to delay this turning point is therefore very significant. We have shown that the use of denosumab in this group of patients can impede the onset of bone metastases by just over four months," says Prof Oudard.

The drug works by inhibiting a protein called RANKL, which is key to the formation of osteoclasts. Unlike osteoblasts, which form bone, osteoclasts are involved in its destruction. If the formation of osteoclasts can be impeded, the bone will remain strong and can continue to hold out against the development of metastases.

The researchers enrolled 1432 men into the trial and randomised them into two groups - one to receive the active drug and the other placebo. They were also encouraged to take calcium and vitamin D supplements for bone health. In July 2010 more than 660 of the patients had either developed bone metastases or had died. The trial was then unblinded and the results analysed.

"We found that denosumab prolonged bone metastasis-free survival significantly as compared with placebo, and that these results were consistent among different sub-groups of the disease and demographic variables such as age, ethnicity, and geographical location. From this we can conclude that, whatever the patient characteristics (initially based on a high prostate specific antigen (PSA) value and/or a short PSA doubling time), denosumab can delay the appearance of bone metastasis. In a condition where there is currently no effective treatment, this is a highly significant finding," Prof Oudard will say.

According to the researchers, patients with bone metastases have an almost five times higher risk of death compared with patients without bone metastases. "Effective therapies are already in place for both early (hormone-sensitive) and advanced (hormone-resistant) prostate cancer, but until now there was a gap in the treatment plan for this group of patients, who are hormone-resistant but have not yet developed metastatic disease," says Prof Oudard.

The trial showed that the adverse effects of the drug were limited, being relatively similar between both the denosumab and the placebo groups. Low blood calcium levels and osteonecrosis of the jaw, a deterioration of the jawbone, were slightly more frequent in the denosumab group, and back pain was the most commonly reported adverse effect in this group.

"Bone is one of the most common places for cancer to spread, and we believe that it is a very fertile environment for tumour cells," says Prof Oudard.

"When cancer spreads to bone, the tumour cells settle in their new micro-environment and continue to grow. Once established, they increase the breakdown of bone, which releases an excess of growth factors back into the blood stream, which then further stimulate tumour growth."

Patients with bone metastases face critical complications. Often the first symptom is pain, which can be severe and debilitating in the majority of patients. Growth of the tumour in the bone weakens the bone itself and puts the patients at risk for serious skeletal-related events (SREs), such as fractures and spinal cord compression. SREs can be profoundly disrupting to a patient's life and strategies to prevent or delay the spread of cancer to the bone can give them a respite from this.

If the osteoclast-mediated bone destruction can be hindered through inhibiting the RANKL protein, the cycle of bone destruction and tumour proliferation can be held back. Given that 90% of men with advanced prostate cancer will have their tumour spread to the bone, the potential advantages of RANKL inhibition are great, the researchers say.

"In this group of patients with castrate resistant prostate cancer, once they have developed bone metastases they are only likely to survive for around two years," says Prof Oudard. "Our trial has shown that denosumab prolongs the period before metastasis where the patients' quality of life has not yet suffered to a great extent. For the first time, we have shown that targeting the bone micro-environment can work in this way. We believe that in future we may be able to do even better by combining denosumab with other targeted treatments," he will conclude.

ECCO President Professor Michael Baumann said: "This is the first large clinical trial to demonstrate that targeting of the bone micro-environment significantly delays onset of bone metastases in hormone resistant prostate cancer patients with high risk for development of bone metastases. What is really striking here is that the effect holds true for all sub-groups of patients evaluated. This offers new options for a considerable group of patients and also will stimulate important further research in this field."

ESMO spokesman Dr. Joaquim Belmunt, from the Medical Oncology Service, Hospital del Mar, Barcelona, said: "Denosumab, being the first agent able to delay the onset of bone metastasis in castrate-resistant prostate cancer, represents a paradigm shift in our beliefs about the limited efficacy of the presently available anti-metastatic strategies. The way this activity will translate into survival benefit will require future investigation."

Provided by ECCO-the European CanCer Organisation