EORTC-NCI-AACR Symposium Press Information

New drug targets vitamin D receptors in hormone resistant prostate cancers: promising results from first clinical trial

A new anti-cancer drug aimed at vitamin D receptors on cancer cells has prompted encouraging responses in the levels of PSA (prostate specific antigen) in men with prostate cancer that has become resistant to hormonal therapies.

Results of the phase II(a) clinical trial will be presented at the 22nd EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Berlin today (Thursday). The trial found that when the new drug, inecalcitol, was combined with the existing, current therapy (docetaxel and prednisone) 83% of patients responded to the treatment with a drop in PSA levels of 30% or more within three months of the treatment. PSA levels are used as a marker for tumour activity and successful treatment shrinks cancer, leading to a drop in PSA levels in the blood.

“The PSA responses with this combination are encouraging,” said Dr Jacques Medioni, who presented the findings. “It compares favourably with historical data showing that normally 65% of patients respond when treated with docetaxel alone. Furthermore, PSA levels declined by 50% in 67% of patients treated with inecalcitol, and biochemical relapse (when PSA levels start to go up again) did not occur for at least 169 days.”

Now inecalcitol is to be tested further in more patients in a larger, phase II(b) clinical trial, which is expected to start in the second quarter of 2011.

Prostate cancer is a chronic disease, usually occurring in men over 50. It is the second most common cancer in men worldwide and an estimated 2.47 million men died from the disease in 2008 worldwide. Initially, male hormones drive the growth of most prostate cancers and so anti-hormonal drugs are effective in stabilising the cancer for several months or years. However, at some point the tumour usually progresses and becomes resistant to anti-hormonal treatments and then it is defined as being hormone-refractory or hormone-resistant prostate cancer (HRPC). Once this happens the prognosis is poor and treatment is currently limited to docetaxel chemotherapy. The average time of survival with HRPC is around 19 months.

Inecalcitol is a novel vitamin D receptor agonist [2], which is extremely effective at inhibiting cancer cell proliferation and differentiation. It is a synthetic derivative of calcitriol, the natural active metabolite of vitamin D3, but it is ten times more potent and one hundred times less toxic than calcitriol.

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Dr Medioni, who is associate professor of medical oncology and head of the Clinical Oncology Centre for Early Trials at the Hôpital Européen Georges Pompidou in Paris (France), and his colleagues in other centres in France enrolled 54 patients in groups of three to six to test the drug for efficacy and toxicity and to discover the maximum tolerated dose.

In this first clinical trial of the drug in HRPC, the patients had an average age of 71, ranging from 49-87; 83% had bone metastases; and the median average PSA levels were 31.7 nanograms per millilitre of blood (ng/ml), ranging from 0.8-962.4 ng/ml. [3]

The researchers found the maximum tolerated dose of inecalcitol was 4000 micrograms a day, as none of the patients treated at this level experienced side effects more serious than mildly raised calcium levels in their blood (hypercalcaemia). Follow-up of a few patients is ongoing, but analysis of 47 patients who were treated with doses up to 2000 micrograms a day showed that PSA levels dropped by 30% or more in 83% of patients within three months of treatment.

“These are really interesting results,” said Dr Medioni. “This study was of a small group of patients and so it is difficult to extrapolate to the wider population of prostate cancer patients; however, the majority of men had very advanced disease and, therefore, it is very encouraging to see PSA levels dropping in such a high proportion of patients and a time to biochemical relapse of nearly half a year. The trial has confirmed that inecalcitol is the first Vitamin D receptor agonist that can be given daily at a high anti-proliferative dose without causing hypercalcaemia.”

A phase II(b) trial to confirm these results is planned for 2011 in centres in Europe and the USA, followed by a multi-centre, randomised, double-blind phase III clinical trial. In addition, work will begin in the near future to evaluate whether inecalcitol may have a role to play in the treatment of early prostate cancer that is still hormone dependent, with the aim of extending the period before the cancer progresses to being hormone-resistant.

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Abstract no: 430. Poster on Thursday 18 November in the Exhibition Hall (ground level) from 08.00/09.00 hrs to 18.00 hrs CET.

Notes:
[1] EORTC [European Organisation for Research and Treatment of Cancer, NCI [National Cancer Institute], AACR [American Association for Cancer Research].
[2] An agonist is a drug that binds to a receptor in a cell and triggers a response by the cell. It often mimics the action of naturally occurring substances.
[3] There is no one PSA reading that is considered ‘normal’. The reading varies from man to man and the normal level increases as you get older. However, they tend to range between 3 ng/ml for a man under 60 to 5 ng/ml for a man over 70.
[4] Worldwide rights to inecalcitol are owned by Hybrigenics (Paris, France), a spin-off company of the Pasteur Institute. It is given to patients as a capsule.
[5] Hybrigenics funded this research.

Further information:
Emma Mason (media information officer)
Tel: +44 (0)1376 563090
Mobile: +44 (0)7711 296 986
Email: wordmason@mac.com