Everolimus plus exemestane improves bone health in post-menopausal women with advanced breast cancer

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Results from a phase III clinical trial evaluating a new treatment for breast cancer in post-menopausal women show that the combination of two cancer drugs, everolimus and exemestane, significantly improves bone strength and reduces the chances of cancer spreading (metastasising) in the bone.

Professor Michael Gnant told the eighth European Breast Cancer Conference (EBCC-8) today that the latest results from the BOLERO-2 trial would change clinical practice. "These results indicate a new standard of care for women with advanced oestrogen receptor positive breast cancer that is resistant to hormonal therapy," he said.

BOLERO-2 had shown previously that the combination of the two drugs significantly improved outcomes, stopping further tumour growth for nearly 11 months, in a group of patients with a form of breast cancer that is highly resistant to treatment. However, as some anti-cancer drugs are associated with reduced bone mineral density and an increased risk of fractures, it was important to discover whether everolimus and exemestane, used with or after treatment with other drugs such as non-steroidal aromatase inhibitors (e.g. anastrozole), affected bone strength.

Prof Gnant, Co-ordinator of the Comprehensive Cancer Centre at the Medical University of Vienna (Vienna, Austria), and colleagues from several different countries looked at markers for bone turnover and bone

resorption (the rate at which bone forms, degrades and renews itself) in the 724 patients enrolled in the trial and randomised to receive either everolimus and exemestane or exemestane alone (the placebo group). The patients had an average age of 62, were from 24 different countries and had been treated previously with aromatase inhibitors. They were enrolled between June 2009 and January 2011, and the researchers assessed three different bone markers at the time of enrolment and after six and twelve weeks.

They found that levels of all three bone markers decreased significantly after six and 12 weeks for women taking everolimus, indicating a low turnover of bone, which improves bone strength and health. After six weeks, bone-specific alkaline phosphatase (BSAP) had dropped by 5.5%, amino-terminal propeptide of type 1 collagen (P1NP) had dropped by 20.4%, and C-terminal cross-linking telopeptide of type I collagen (CTX) had dropped by 6.3%. After 12 weeks, they had decreased by 3.6%, 26.8% and 0.5% respectively. In the placebo group they all increased.

Overall, out of all the women in the trial, only 3% of the women taking everolimus had further bone metastases after 60 days, compared with 6% in the placebo group; in a sub-group of women who were known to have bone metastases at the start of the trial, everolimus halved the rate of further bone metastases, with bone metastases progressing in nearly 4% of these women, compared to 8% in the placebo group. This trend continued for longer than six months. Any bone-related side effects were rare and those that did occur were of a low grade, including bone pain and fractures.

Prof Gnant said: "These results show that the addition of everolimus to exemestane is greatly beneficial to bone health by reducing bone turnover and improving time to bone metastases. Everolimus appears to make it more difficult for metastases to occur and grow in bone.

"In addition to the spectacular effect on outcomes and time to progression, both in bone and elsewhere, improving bone health is an important aspect of giving patients the best possible treatment. We would now recommend everolimus, in addition to exemestane, for all post-menopausal women with hormone-resistant advanced cancer until further progression of their cancer.

"The interesting question we would like to address now is the effect of everolimus in women with early breast cancer, where bone health may be an even more important issue. Currently, clinical trials to investigate this are being designed."

Professor David Cameron, from the University of Edinburgh (Edinburgh, UK), and chair of EBCC-8 said: "This study has already demonstrated that resistance to endocrine therapy can be overcome by using medicine to block the way breast cancer cells escape from endocrine therapy. These new data show that this additional treatment has beneficial effects on bone health, the full implications of which are not yet clear."

The hormone oestrogen promotes the growth of about two thirds of breast cancers, and hormonal therapies such as exemestane are used to treat these hormone receptor-positive breast cancers. However, many breast cancer patients and nearly all patients with advanced breast cancer that has metastasised to other parts of the body become resistant to hormonal therapy. When patients stop responding to hormonal therapy, the benefits from any secondary therapy are limited.

Exemestane is currently used to treat women who have metastatic breast cancer and women whose breast cancer has returned after initial treatment. It is also used to treat women with early breast cancer after they have completed two or three years of treatment with another hormonal therapy, tamoxifen.

Everolimus is an inhibitor of the mTOR protein, which has a number of roles, including regulation of cell growth, proliferation, motility and survival. It is an established treatment for recurrent, advanced kidney cancer and researchers are now looking at its use in other cancers. The BOLERO-2 trial was set up to investigate the efficacy of everolimus, in combination with exemestane, in patients who have become resistant to aromatase inhibitors – drugs that decrease the amount of oestrogen produced and help to slow or reverse the growth of the cancer, but which are also known to have an adverse effect on bone health.

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