# Bone drug is mixed blessing for breast cancer patients

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A drug used to protect bone may extend survival in older breast cancer patients, according to researchers at the Universities of Sheffield and Leeds.

The AZURE trial has revealed that the bisphosphonate drug zoledronic acid boosts disease-free survival in postmenopausal breast cancer patients but may have an adverse effect on younger women.

The full results of the trial were presented at the European Multidisciplinary Cancer Congress in Stockholm on Sunday 25 September and published simultaneously in the New England Journal of Medicine.

Bisphosphonate drugs, like zoledronic acid, are used mainly to treat osteoporosis.

However, they may also be given to breast cancer patients to protect against the effects of secondary bone cancer.

The trial, which started in 2003, involved 3,360 women with early breast cancer from 174 centres in the UK, Australia, Spain, Ireland, Portugal, Taiwan and Thailand. Patients were randomised to receive standard chemotherapy and/or endocrine therapy (hormone therapy) for their breast cancer, to try and prevent recurrence or spread of the disease, with or without zoledronic acid.

Contrary to previous studies, there was no significant difference in disease-free or overall survival between patients who received zoledronic acid and those that did not, looking at the study population as a whole.

However, the addition of zoledronic acid did bring significant benefits to an important subgroup of women within the trial.

The study revealed that women who had completely passed through the menopause (five years since last period) had significantly improved disease-free and overall survival.

Here, the overall survival rate at five years was 85 per cent compared to 79 per cent for women who did not receive zoledronic acid.

The benefit was independent of the characteristics of the disease as defined by the stage of the tumour, oestrogen receptor status, and lymph node involvement.

For all other patients, overall five year survival was similar at 86 per cent in the zoledronic acid group and 85 per cent in the control group.

Most surprisingly, it was the recurrence rates outside bone that were most profoundly affected by the zoledronic acid with clear benefit in the postmenopausal women but a possible adverse effect in younger women.

The relative risk for developing metastases outside bone during treatment with zoledronic acid was approximately halved in the postmenopausal women compared with the younger patients (p <.001).

The results shed new light on the role that the bones may play in the progress of the disease.

The effects on metastasis and recurrence outside bone suggests that the bone marrow is an important sanctuary for tumour cells which can be activated after sometimes many years of dormancy.

With help from bone marrow stem cells, these previously dormant tumour cells may then spread via the blood stream to set up metastases at other sites.

Other studies in postmenopausal women and younger women given treatment to induce a menopause with hormone sensitive breast cancer have also indicated benefit for zoledronic acid in early breast cancer.

The AZURE trial is the first study to evaluate the use of zoledronic acid in a broad range of patients.

Further data from other similar trials are anticipated later this year.

Professor Robert Coleman from the University of Sheffield, who led the study, said: "The results have shown that zoledronic acid should not be used routinely for the treatment of early breast cancer.

However, for those with low levels of female hormones, due either to natural ageing or specific treatments to induce menopause, the approach appears very promising as more women go on to rid themselves of the disease.

"Our findings could mean a major new treatment approach for the tens of thousands of women in the UK who develop breast cancer.

We are now investigating the hormone levels in blood and the biology of the breast tumours in samples donated by the AZURE patients to help us better understand the reasons behind our results."

Helen Marshall, Principal Statistician from the University of Leeds' Clinical Trials Research Unit (CTRU), said: "The statistics of this analysis are complex and the results need to be interpreted with a degree of caution.

The size and significance of the difference by menopausal status suggests that this finding is genuine, but we will need to carry out further studies to substantiate this exciting result."

The AZURE trial was led by Professor Robert Coleman from the University of Sheffield.

The University of Leeds' Clinical Trials Research Unit (CTRU) was responsible for data management and statistical analysis of the data.

The project was funded by pharmaceutical company Novartis, who provided a £6million grant to the University of Sheffield to run this study in collaboration with the National Cancer Research Network.

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To see the results of the AZURE trial in the New England Journal of Medicine, go to <http://www.nejm.org/>.