



Media Release

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New treatment produces better outcomes for women with early breast cancer

New clinical trial results show for the first time that a better outcome is produced by extending treatment with the drug letrozole (Femara[®]) beyond the standard five years of tamoxifen for postmenopausal women with oestrogen receptor positive early breast cancer.

The international trial, MA-17, was conducted by the National Cancer Institute of Canada Clinical Trials Group in collaboration with other collaborative breast cancer trials groups.

The current standard of treating women with oestrogen receptor positive early breast cancer is five years of treatment with tamoxifen after initial treatment with surgery and radiotherapy. On average, five years of postoperative treatment with tamoxifen reduces the risk of breast cancer recurrence by 47% and death by 26% compared with surgery and radiotherapy alone.

In the MA-17 trial, 5,187 postmenopausal women who had an oestrogen receptor positive breast cancer and who had completed five years of treatment with tamoxifen were then randomised to receive no further treatment (placebo) or five years of further treatment with the aromatase inhibitor letrozole.

In MA-17 the additional treatment for the planned further five years with letrozole, produced a highly significant improved disease free survival, compared to the initial five years of tamoxifen alone (four year disease free survival: tamoxifen for five years followed by letrozole, 93%, versus tamoxifen alone for five years, 87%, $p < 0.00008$).

Professor John Forbes, Group Coordinator of the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) said: "These results are good news. They have important implications for several thousand women in Australia and for our national clinical trials research program. It is a genuine advance".

The ANZ BCTG is Australia's national breast cancer research group conducting clinical trials for the treatment and prevention of breast cancer.

How letrozole works

Many breast cancers are stimulated to grow by the natural hormone oestrogen. Tamoxifen, the current standard treatment, works by blocking the effect of oestrogen on breast cancer cells. A new class of anti-cancer drugs called aromatase inhibitors work by reducing the production of oestrogen in postmenopausal women thus depriving cancer cells of the source of oestrogen. Letrozole is an aromatase inhibitor. A prior, large clinical trial has shown that the aromatase inhibitor anastrozole is superior to tamoxifen as the initial treatment for early breast cancer for the first five years of treatment.

Trial stopped early

The MA-17 trial was stopped early on the recommendation of the Independent Data Monitoring Committee, because of significant positive results at the first planned interim analysis. The continued treatment with letrozole showed a highly significant advantage in disease free survival (75 new breast cancer events on the letrozole arm, 132 on the placebo arm) with a projected four year disease free survival of 93% (tamoxifen for five years followed by letrozole) and 87% (tamoxifen alone for five years), $p < 0.0008$. The advantage for letrozole appeared to be present for women who had involved lymph glands and for those who did not.

There were 42 deaths (17 breast cancer deaths) on the placebo arm and 30 deaths (9 breast cancer deaths) on the letrozole arm.

Well tolerated drug

The letrozole was well tolerated by women and most toxicities were low grade. Toxicities increased on letrozole compared with placebo were hot flushes (19% versus 16%), arthralgia (16% versus 15%) and myalgia. Vaginal bleeding was significantly less common with letrozole. There was a trend towards an increased rate of osteoporosis for women on the letrozole arm although the difference was small (3.6% versus 2.9%). More bone fractures were reported for letrozole (3.6% versus 2.9%, $p=0.07$) but the difference was not significant.

? A prevention role for aromatase inhibitors

An important finding was that the patients taking letrozole had less new breast cancers in the opposite breast (14 versus 26, 46% reduction). A similar effect for tamoxifen, noted in the past, was the first evidence that tamoxifen might prevent breast cancer in women at high risk. This prevention role for tamoxifen has since been established.

“Our long term goal is prevention. The MA-17 results showing a reduction in contralateral breast cancers are very encouraging for a prevention role for aromatase inhibitors. The ANZ BCTG will shortly commence an international prevention trial for postmenopausal women at increased risk of breast cancer testing the aromatase inhibitor anastrozole” said Professor Forbes.

Limitations of the results

The MA-17 trial was stopped early because of the highly significant results and the potential importance for women. At this point however, only 23 patients had completed follow up to four years or beyond. Patients who were on the placebo are now to be offered further treatment with letrozole, although the trial does not provide any information about the value of letrozole after an interval between completing tamoxifen and starting letrozole.

At this point no significant survival data has been obtained and now may not be obtained reliably in the future, given that unbiased follow up will not be continued (women on placebo are to be offered letrozole). It is unfortunate that survival data may not be obtained but this seems unavoidable. Nevertheless, the data remains highly significant and is very important. Published results from the ATAC Trial¹ established that the aromatase inhibitor anastrozole is superior to tamoxifen for first line treatment of early breast cancer in a similar population. Hence, taken together, the two trials clearly indicate a new role for aromatase inhibitors for the treatment of oestrogen receptor positive early breast cancer in postmenopausal women.

New questions

At this stage it is not possible to determine whether the improved outcome with added letrozole is due to the longer treatment period, the switching from tamoxifen to letrozole after five years, or both. Other studies testing a longer duration of tamoxifen alone for more than five years have not shown an advantage for the longer treatment beyond five years. Hence the addition of the letrozole is probably the critical component.

Clinical trials being conducted in Australia by the ANZ BCTG are already testing continuous treatment of tamoxifen versus a switch of treatment within the first five year period. Trial ANZ BCTG / IBCSG 18 (BIG 1-98)² now has heightened importance; it has completed recruitment of more than 7,000 women worldwide and will provide data in early 2005. The four treatments in this trial are (i) five years of tamoxifen, (ii) five years of letrozole, (iii) two years of tamoxifen followed by three years of letrozole, and (iv) two years of letrozole followed by three years of tamoxifen.

The reduction in contralateral breast cancer rates with letrozole is potentially a very important finding for future breast cancer prevention. This reduction suggests that the aromatase inhibitor letrozole might be able to prevent new breast cancer. The ANZ BCTG prevention trial, IBIS II, uses the aromatase inhibitor anastrozole against placebo for postmenopausal women at increased risk of breast cancer. This trial is now a very high priority research project worldwide.

The increased rate of osteoporosis and fractures with letrozole is important but unlikely to present a difficult clinical problem. Osteoporosis can be readily treated and is preventable in women at risk by use of bisphosphonates. The risk of osteoporosis in breast cancer patients in various settings, e.g. premenopausal women who have chemotherapy, is being more widely recognised, and breast cancer patients being treated with aromatase inhibitors should be also recognised as a group at risk. This requires further investigation.

Implications for treatment and advice for women

Currently about 1 million women worldwide are taking a planned five years of tamoxifen for treating early breast cancer. Approximately 20,000 women in Australia are taking tamoxifen in this setting. The results of the MA-17 trial are potentially important for these women.

Women currently taking tamoxifen should discuss their ongoing care with their breast cancer specialist. Letrozole is available on prescription on the Pharmaceutical Benefits Scheme (PBS) for treating advanced breast cancer but is not subsidised by the PBS for this new use.

Postmenopausal women who have previously completed their five years of tamoxifen treatment for early breast cancer and who are now free of disease, do not need to consider this new treatment.

Implications for current clinical trials in Australia

Recently, the ANZ BCTG helped complete the international overview of the tamoxifen prevention trials for women at increased risk of breast cancer. This overview showed that tamoxifen can prevent breast cancer but with rare, potentially serious, side effects (thromboses and endometrial cancer). These side effects have not been seen with the aromatase inhibitors. The new IBIS II prevention trial using the aromatase inhibitor anastrozole, to avoid the serious side effects seen with tamoxifen, now has high international priority.

The ANZ BCTG is currently conducting further international trials of aromatase inhibitors to determine their most appropriate place in the treatment of early breast cancer. These trials have enhanced importance in the light of results from MA-17.

“The results from MA-17 highlight the importance of ongoing ANZ BCTG trials with aromatase inhibitors. It is important to acknowledge that the few thousand women who participate in such clinical trials, contribute to better outcomes, potentially for millions of women worldwide” concluded Professor Forbes.

Notes:

1. ATAC Trial – The largest international adjuvant clinical trial. Conducted in Australia by the ANZ BCTG. Compares five years of tamoxifen with five years of anastrozole in postmenopausal women with oestrogen receptor positive breast cancer. Anastrozole was shown to be significantly superior for disease free survival after four years of follow up.
2. ANZ BCTG / IBCSG 18 (BIG 1-98) – International Breast Cancer Study Group 18. Conducted in Australia by the ANZ BCTG. Compares five years of tamoxifen with five years of letrozole, and two years of tamoxifen followed by three years of letrozole, and two years of letrozole followed by three years of tamoxifen in postmenopausal women with oestrogen receptor positive breast cancer. Results expected in 2005.

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