



Media Release

9 June 2004

New treatment approach produces better outcome for women with early breast cancer.

Updated results from a clinical trial presented today (June 8) in the United States confirms that additional treatment with the drug letrozole after the standard five years of treatment with tamoxifen improves outcomes for postmenopausal women who have had early hormone sensitive breast cancer.

The trial, MA-17, was conducted by the National Cancer Institute of Canada Clinical Trials Group with international collaboration with other breast cancer trials groups. The new data was presented by the Study Leader, Dr Paul Goss, in the "Best of Oncology" session at the annual meeting of the American Society of Clinical Oncology in New Orleans.

The current standard of treating women with hormone sensitive (hormone receptor positive) early breast cancer, after initial local treatment with surgery and radiotherapy, is five years of treatment with tamoxifen. 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 a hormone receptor positive breast cancer and who had completed five years of treatment with tamoxifen were then randomised to receive placebo (no further active treatment) or a scheduled five years of additional treatment with the aromatase inhibitor letrozole.

In MA-17 the additional treatment with letrozole for a scheduled further five years after tamoxifen, 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%, $p < 0.00008$). This positive result led to early stopping of the trial in late 2003.

The updated analysis included new events (relapses, deaths and side effects) that had either occurred at the time of the first analysis but had not yet been reported or which had occurred since the first analysis.

In the updated analysis, a significant mortality benefit was observed for the stratum of women who had involved lymph glands at the time of diagnosis (node positive patients) – 45 deaths in the group who stopped therapy at five years versus 29 in the group who continued on the letrozole ($p = 0.035$). In the previous analysis, no significant mortality effect was found. In addition, the previously reported significant reduction in metastatic breast cancer recurrences was confirmed with a median follow-up of 2.5 years.

Professor John Forbes, Group Coordinator of the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) said: "These results are important for postmenopausal women with hormone sensitive breast cancers. Until now these women have had drug treatment limited to five years of tamoxifen, and although most such women remain disease-free long term, about 2-3% of these women relapse with recurrent breast cancer each additional year of follow-up. With additional letrozole after tamoxifen the relapse rate was significantly reduced, and the new analysis confirms that this is true separately for both node positive ($p = 0.007$) and node negative patients ($p = 0.002$). The benefit was also seen whether or not the patient treatment included chemotherapy ($p = 0.003$)."

“The overall survival advantage was not significant (51 deaths versus 62). However there was a significant reduction in deaths of 40% for women who had involved lymph nodes at diagnosis (28 deaths versus 40). Patients with involved lymph nodes were a separate strata in the trial. This is important, as it is in this node positive group of patients where we expect to see the first evidence of a true effect and that is the finding that has been reported for this trial” Professor Forbes said.

Professor Forbes stressed that although the results are heartening for women and researchers, the follow-up is brief (2.5 years) and there is no significant overall reduction in deaths at this stage.

“It is clear that these aromatase inhibitor drugs are superior to tamoxifen for some patients. We need longer follow-up to confirm effects on mortality for all patients and to reliably establish the side effect profile” said Professor Forbes.

The ANZ BCTG is Australia’s national breast cancer research group conducting clinical trials for the treatment and prevention of breast cancer. Current trials are testing whether use of letrozole from diagnosis and also whether sequencing tamoxifen and letrozole in the first five years might be beneficial. Other trials conducted by the ANZ BCTG have demonstrated that anastrozole, a similar type of drug to letrozole, used from the time of diagnosis, is superior to tamoxifen.

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. The 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 showed that, with a median follow-up of four years, the aromatase inhibitor anastrozole is superior to tamoxifen as the initial treatment for early breast cancer for the first five years of treatment.

Well tolerated drug

In the initial report, letrozole was well tolerated by women and most toxicities were low grade. Toxicities increased on letrozole compared with placebo were hot flushes and myalgia. Vaginal bleeding was significantly less common with letrozole. In the updated analysis, the incidence of osteoporosis was significantly increased (8% versus 6%, $p=0.03$). More bone fractures were reported for letrozole (3.6% versus 2.9%), but the difference was not significant ($p=0.07$).

Limitations of the results

The MA-17 trial was stopped in late 2003 because of the highly significant results and the potential importance for women. After the first results appeared some patients in the placebo group were offered letrozole, hence long term follow-up to assess benefits and side effects will be incomplete.

Nevertheless, the data remains highly significant and 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. More recently, the IES Trial² showed that switching to an aromatase inhibitor (exemestane) earlier – after two to three years of tamoxifen – also was superior to five years of tamoxifen alone. Hence, taken together, the three trials clearly indicate an important role for aromatase inhibitors for the treatment of oestrogen receptor positive early breast cancer in postmenopausal women.

A prevention role for aromatase inhibitors?

An important finding was that the patients taking letrozole had less new breast cancers in the opposite breast (19 versus 30). 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 is conducting an international prevention trial (IBIS II) for postmenopausal women at increased risk of breast cancer testing the aromatase inhibitor anastrozole” said Professor Forbes.

ADDITIONAL NOTES

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)³ 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, is testing the aromatase inhibitor anastrozole against placebo for postmenopausal women at increased risk of breast cancer. This trial is 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 some of these women when they complete their five years of tamoxifen.

Women currently taking tamoxifen should discuss their ongoing care with their breast cancer specialist.

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

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.

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 the latest analysis of MA-17.

“The updated 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. The Lancet 2002;359:2131-39.
2. IES Trial – Intergroup Exemestane Study. Conducted in Australia by the ANZ BCTG. Compared tamoxifen for two to three years followed by exemestane to complete the five years, versus five years of continuous tamoxifen in postmenopausal women with oestrogen receptor positive breast cancer. Tamoxifen followed by exemestane was shown to be significantly better than continuous tamoxifen with less recurrences and less new cancers in the opposite breast with short term follow-up.
N ENGL J MED 2004;350:1081-92.
3. ANZ BCTG / IBCSG 18 (BIG 1-98) – International Breast Cancer Study Group 18. Is being 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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