



## Supporting Evidence

Recently there have been a number of trials that have studied the role of aromatase inhibitors in the adjuvant (early) treatment of breast cancer. These drugs, which are frequently used in relapsed disease, are powerful inhibitors of the enzyme aromatase which converts testosterone to estrogen. This pathway is the major source of estrogen production for postmenopausal women. The three available inhibitors are anastrozole (Arimidex®), letrozole (Femara®) and exemestane (Aromasin®) and all appear to have a possible role in the adjuvant treatment of postmenopausal women with invasive hormone sensitive breast cancer. The very best way to use these treatments is not yet known.

Studies using adjuvant tamoxifen for more than 5 years did not show a benefit to extended therapy, but the benefit of “extended adjuvant therapy”, using an aromatase inhibitor after 5 years of tamoxifen, was clearly demonstrated in the MA-17 trial, sponsored by the National Cancer Institute in Canada and conducted throughout Canada, the United States and Europe.

This randomized placebo-controlled trial, which involved over 5000 women, was designed to test the effectiveness of 5 years of therapy with letrozole (Femara) in postmenopausal women with breast cancer who had already completed 5 years of tamoxifen therapy. At the first stage analysis (approximately 2.4 years), 75 women in the letrozole group and 132 women in the placebo group had a local or metastatic recurrence of breast cancer or new primary cancer in the contralateral breast, corresponding to a relative risk reduction of 43% in the letrozole arm (absolute risk reduction of 6%). The estimated 4-year disease-free survival rate was 93% in the letrozole group and 87% in the placebo group.

The letrozole group had a slightly higher incidence of new diagnoses of osteoporosis, though rates of fracture were similar in both groups. Few women discontinued the study because of adverse effects.

The MA-17 trial’s results led the independent data and safety monitoring committee to recommend that the trial be terminated early and the results communicated to participants. The study when reported in the New England Journal of Medicine, showed that letrozole therapy after the completion of standard tamoxifen treatment significantly improved disease-free survival, and a recent updated analysis showed a modest overall survival benefit in node positive women.

On the basis of these findings, we now have approval and funding in British Columbia and are able to offer postmenopausal women with ER-positive tumours treatment with letrozole after completing 4.5 - 5 years of tamoxifen therapy. At this time, the recommended duration of letrozole therapy is 3 years, although this may be revised with further information.

Women who are eligible for letrozole should have a discussion about the relative risks and benefits to them of treatment. As breast cancer can relapse even many years after a diagnosis, there is merit in considering further treatment, but a recommendation should be tailored to the individual woman, as each woman’s risk of relapse is related to the risk of the initial tumour. We have looked at the BC data base and women with small, low grade tumours that do not involve the lymph nodes have such a low risk of relapsing that the risks of taking letrozole may outweigh the benefits. As well, the health status of the woman should be considered in terms of her other competing health risks over the next 5 years and in terms of the side effects of letrozole, which include an increased risk of osteoporosis and a potential increase in lipid levels. The benefit of letrozole for women who have completed tamoxifen more than one year ago is not known and therefore this is not being recommended or routinely covered at this time. As well, this treatment is not indicated for women who have already been treated with an aromatase inhibitor instead of tamoxifen or for women who are not postmenopausal.

Reference: N Engl J Med. 2003 Nov 6;349(19):1793-802