

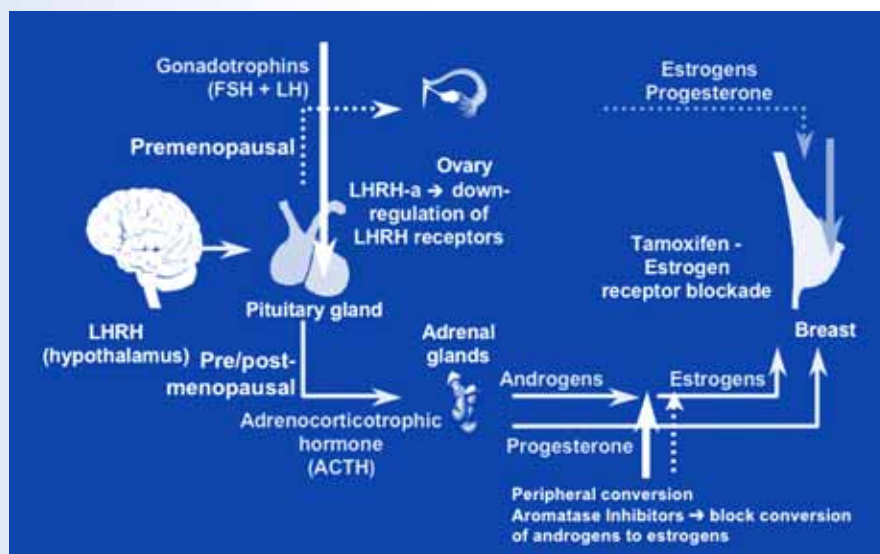
Recommendations for Hormonal Therapy of Surgically-Treated, Endocrine-Responsive Invasive Breast Cancer

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Background

Hormonal therapy has been a cornerstone in the adjuvant treatment of surgically resected breast cancer that has measurable estrogen and/or progesterone receptors (ER and/or PR). The Early Breast Cancer Trialists Group has documented a highly significant advantage favouring five years of tamoxifen versus placebo for disease free- and overall survival [1]. The National Surgical Adjuvant Breast and Bowel Program (NSABP) has documented no additional benefit of extending tamoxifen use to ten years as compared to five [2]. Toxicities of tamoxifen are modest but can include an increased risk of thromboembolism as well as a slightly higher risk of endometrial hyperplasia/malignancy in women with an intact uterus. Benefits of tamoxifen can include a protective effect on post-menopausal bone loss and a reduced risk of osteopenia/osteoporosis.

The advent of the aromatase inhibitors has resulted in efforts to incorporate these new agents in the adjuvant therapy of ER and/or PR positive breast cancer in the post-menopausal population. Aromatase inhibitors, by reducing circulating endogenous estrogen levels by 95-98% in post-menopausal women, deprive the ER and/or PR positive breast cancer cell of its major growth factor (estrogen). They have all been compared to megestrol acetate for the second-line



Mechanisms of Estrogen Production and Blockade

therapy of metastatic breast cancer, and versus tamoxifen in first-line therapy. Results from all trials have firmly established these agents in breast cancer management from both an efficacy and toxicity standpoint. The three agents in general use are: anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin). The former two are non-steroidal agents, which act as classic inhibitors of the aromatase enzyme. The latter compound is steroidal in nature and results in down-regulation or inactivation of the aromatase enzyme. All three exhibit target specificity and have no impact on steroidogenesis [3,4].

Recently, anastrozole (Arimidex) has been compared to tamoxifen as adjuvant

hormonal therapy for post-menopausal women following surgery (Arimidex versus Tamoxifen alone and in Combination - ATAC). Evolving results, at a median follow-up time of 68 months reveal a 3.3% absolute disease-free survival (DFS) advantage favouring anastrozole for those women with ER and/or PR positive breast cancer. Events included in the DFS analysis were: local recurrence, distant recurrence, contralateral breast cancer and deaths before disease recurrence. No difference in overall survival has been observed to this point. Anastrozole was associated with fewer episodes of venous thromboembolism (2.8% vs. 4.5%, $p=0.0004$) but more bone fractures (11% vs. 7.7%, $p<0.0001$) compared to tamoxifen [5,6].

Background (continued)

The MA-17 trial compared five years of letrozole (Femara) to placebo following completion of five years of adjuvant tamoxifen in postmenopausal women [7,8]. At the first planned interim analysis, with a median follow-up of 2.4 years, a statistically significant difference favouring letrozole for disease-free survival was observed.

The absolute difference in favour of letrozole was 2.2% and included local-regional recurrence, contra-lateral new primary cancers, as well as the development of distant metastases. The estimated absolute difference in the four-year DFS rate was 4.8% for the entire group. A pre-planned analysis of node-negative versus node-positive patients revealed an estimated four-year DFS rate of 2.4% versus 7.5% respectively.

Overall survival was significantly impacted in the node-positive population but not in the node-negative population nor in the overall study population. There were more new cases of self-reported osteoporosis in the letrozole group (8% vs 6%, $p=0.003$) but no difference in fracture rate.

Results from a trial comparing five years of adjuvant tamoxifen to 2-3 years of tamoxifen followed by completion of five years of therapy with exemestane (Aromasin) have also been recently published (Intergroup Exemestane Study - IES) [9].

At a median follow-up time of 30.6 months, an absolute benefit of 4.7% was observed favouring the sequential therapy arm. Events included in the DFS analysis were: local recurrence, distant recurrence, contra-lateral breast cancer, as well as inter-current death without disease recurrence.

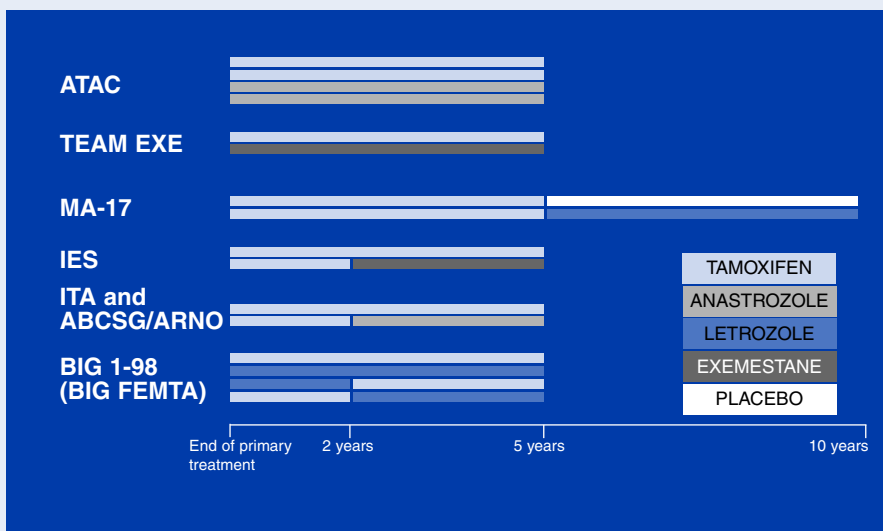
There was no statistically significant difference in overall survival. There were more new cases of osteoporosis in the sequential arm (7.4% versus 5.7% $p=0.05$), as well as more diarrhea (4.3% versus 2.3%, $p<0.001$).

Two other large, multi-centre, randomized-controlled trials have also very recently been presented. The Breast International Group (BIG) 1-98 trial included four treatment arms; either tamoxifen or letrozole for five years or tamoxifen or letrozole for two years

followed by a switch to the other agent to complete five years. At a median follow-up of 25.5 months, and comparing only those that had either of the two agents alone, a 2.6% absolute difference in disease-free survival was observed [10]. As well, the Austrian Breast Cancer Study Group (ABCBSG) examined the sequence of tamoxifen for two years followed by anastrozole for three years, compared to tamoxifen for five years.

With a median follow-up of 28 months, a statistically significant event-free survival advantage was observed for the sequence [11]. The latter trials were only presented in abstract form at the time of writing.

At the time of writing there have been approximately 27,273 post-menopausal woman randomized to an adjuvant strategy including aromatase inhibitors. The preponderance of evidence strongly suggests that aromatase inhibitors may have an important role in adjuvant therapy programs for post-menopausal women with ER and or PR positive, surgically-treated breast cancer [12]. At this point, the optimal strategy remains unidentified and future trials will be needed. As well, long-term toxicities remain to be fully elucidated.



Current Trial Strategies of AIs in the Adjuvant setting

Recommendation Summary

Premenopausal women: Tamoxifen alone, or following systemic chemotherapy is an option for all women, for whom further risk reduction is indicated, following surgical resection of ER and/or PR positive invasive breast cancer.

Postmenopausal women: Either tamoxifen or anastrozole, alone or following systemic chemotherapy are options for all postmenopausal women, for whom further risk reduction is indicated, following surgical resection of ER and/or PR positive invasive breast cancer. The choice of hormonal therapy may be based on absolute and perceived risks and benefits in the context of other medical co-morbidities, patient preference and/or cost. If anastrozole is chosen, subsequent use of letrozole following five years of anastrozole is NOT recommended.

Postmenopausal women after 2-3 years of tamoxifen: Consideration may be given to switching to exemestane after two to three years of exposure to tamoxifen. It is important to note that the long-term benefit of this strategy remains unknown and must be compared to the observed overall survival benefit, as well as the durability of benefit noted for five years of tamoxifen. The decision to proceed with this approach may be based on absolute and perceived risks and benefits in the context of ongoing tolerance of tamoxifen, medical co-morbidities, patient preference and/or cost. If a decision is made to choose sequential therapy, subsequent use of letrozole following two to three years of exemestane is NOT recommended.

Premenopausal women - adjuvant hormonal therapy following five years of tamoxifen:

There is no recommendation for further systemic hormonal adjuvant therapy in this patient population. Specifically, neither ovarian ablation nor the use of aromatase inhibitors is routinely recommended.

Postmenopausal women - adjuvant hormonal therapy following five years of tamoxifen:

Further (extended) adjuvant therapy with letrozole following five years of tamoxifen can be recommended as an option. The choice of whether to proceed with extended letrozole may be based on absolute and/or perceived risks and benefits in the context of other medical co-morbidities, the baseline risk of recurrence of the initial breast cancer, patient preference and/or cost. The optimal time interval between discontinuing tamoxifen and beginning letrozole therapy is unknown. In general, patients may begin letrozole up to one year following completion of tamoxifen. A longer therapy-free interval may be reasonable for motivated patients.

These recommendations will be revised as further data becomes available. Important data not fully available yet includes:

- Mature overall survival results from the major trials
- Long-term toxicity results from the major trials
- Relevant sub-study results (quality of life, bone, lipids)
- Results from The ATLAS trial (five versus 10 years of tamoxifen) and the Atom trial (five versus more than five years of tamoxifen).

General Recommendations

- Benefit and risk should be discussed using absolute differences whenever possible.
- There was no significant difference in incidence or severity of hot flash symptomatology in the IES trial examining switching to exemestane after two to three years of tamoxifen, compared to continuing tamoxifen for five years. Therefore, the severity or incidence of hot flashes should not be the sole factor in recommending switching to an aromatase inhibitor.
- All discussions should take place within the context of a supportive environment, whenever possible, with all decisions supported.
- All women receiving adjuvant aromatase inhibitor therapy should be counseled on the optimal doses of Vitamin D (800 IU/day) and calcium (1500mgs/day) to aid in the prevention of osteopenia/osteoporosis.
- Bone mineral density evaluation may aid in the decision making process as to choice and sequence of adjuvant hormonal therapies and may be useful in the ongoing evaluation of bone health for women on long-term aromatase inhibitor therapy.
- Due to the evolving and currently incomplete nature of clinical trial data in the adjuvant hormonal therapy of ER and/or PR positive breast cancer, consideration should be given to scheduling a routine follow-up appointment with medical oncology for those women who would otherwise be discharged to community follow-up. It is suggested that this appointment should be at approximately the two-year mark of initiation of adjuvant hormonal therapy.

Cancer Care Nova Scotia is a program of the Department of Health. Its mandate is to evaluate, coordinate and strengthen the cancer system in Nova Scotia.

Cancer Care Nova Scotia works with and supports professionals and stakeholders in the health care system to bring about patient-centred change. Its ultimate goal is to reduce the burden of cancer on individuals, families, communities and the health care system.

In Practice is a supplement to *Cancer Care Nova Scotia's* newsletter. It is written specifically for primary care practitioners with information that we hope will make a difference in your cancer practice.

Please contact Christine Smith, Communications Coordinator, *Cancer Care Nova Scotia*, by phone at 902-473-2932 or by email at christine.smith@ccns.nshealth.ca with comments or suggestions for future topics.



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