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New guidelines for treatment of early hormone-positive breast cancer with tamoxifen and aromatase inhibitors

Three strategies can be used to incorporate aromatase inhibitors in adjuvant therapy for postmenopausal breast cancer patients.

ABSTRACT: The Breast Tumour Group of the British Columbia Cancer Agency has developed new treatment guidelines for the use of tamoxifen and the aromatase inhibitors anastrozole, letrozole, and exemestane. These guidelines are based on recent evidence about the role of these agents in adjuvant therapy for women with hormone-positive breast cancer. Physicians should be aware of the data supporting the adjuvant use of tamoxifen and aromatase inhibitors and the new policies regarding their use. Depending on the grade and size of the tumor and the number of positive nodes, postmenopausal women with early invasive breast cancer may receive tamoxifen monotherapy, aromatase inhibitor monotherapy, or sequential therapy. The BC Cancer Agency has informed patients and health care providers of these policies by letter. Further information is available under "Cancer Management Guidelines" at www.bccancer.bc.ca.

The Breast Tumour Group, a provincial multidisciplinary committee of the British Columbia Cancer Agency (BCCA), has developed new guidelines for the use of tamoxifen and aromatase inhibitors (AIs) in adjuvant therapy for early hormone-positive breast cancer in postmenopausal women. Physicians are encouraged to adhere to these treatment protocols (see **Figure 1**) and should request undesignated approval prior to prescribing tamoxifen or AIs outside of the guidelines. When prescribed within the guidelines, these medications are all funded by the BCCA.

Hormone-positive breast cancer

In British Columbia, every primary breast cancer is tested for estrogen receptor (ER) positivity and approximately 70% are ER-positive. Hormonal therapy and, possibly, radiation and chemotherapy, are offered after surgery to women with ER-positive tumors with a risk of recurrence.

Since its introduction in the 1970s, tamoxifen has been the most important advance in the management of ER-positive breast cancer. Tamoxifen is a selective estrogen receptor modulator (SERM) and inhibits the growth of breast cancer cells by competitive antagonism of estrogen at its receptor. Daily tamoxifen for 5 years reduces the risk of breast cancer death by 31%, regardless of age or use of chemotherapy.[1,2] This benefit is sustained even at 15 years from initial diagnosis.[2]

Although well tolerated by the majority of women, tamoxifen is associated with a number of side effects that are related to its dual agonist and antagonist activity. Side effects include hot flushes, gynecological symptoms such as vaginal discharge, risk of uterine cancer (1%), thromboembolic disease, and stroke. The absolute risk of death from thromboembolic and uterine cancer due to tamoxifen is 0.2% per decade, which is small compared with the absolute benefits.[2] In postmenopausal women only, tamoxifen is associated with beneficial effects on

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Strategies for incorporating aromatase inhibitors in adjuvant therapy for breast cancer

n Postmenopausal women

Strategy A: Tamoxifen monotherapy

For patients with low-grade node-negative tumors <2 cm and no evidence of lymphatic or vascular invasion

- Tamoxifen for 5 years
- Substitution of an AI allowed if patient is intolerant of tamoxifen or if serious complications occur or if contraindications exist

Strategy B: AI monotherapy

For patients at high risk of early relapse, defined as having breast cancer that is:

- High grade (grade 3/poorly differentiated) or
- Low ER-positive (1+) or
- Stage III (includes breast cancers with four or more nodes positive, or large node-positive tumors, or that present with locally advanced breast cancer)
- May consider using first-line AI therapy for 5 years

Strategy C: Sequential therapy

For patients with all other tumors

- Tamoxifen for 2–3 years followed by AI for 2–3 years, for total 5 years of hormonal therapy ("early switch")

For patients who have finished >3 years of tamoxifen already at this time, or who become postmenopausal *after* completing 3 years of tamoxifen

- Tamoxifen for 5 years followed by AI for 3–5 years ("late switch")

n Premenopausal women

- Tamoxifen for 5 years unless patient becomes postmenopausal during therapy (no menses >12 months and FSH/LH in postmenopausal range), in which case, see Strategy C above

Figure 1. Summary of BCCA Breast Tumour Group guidelines.

bone health and on lipid profile. Raloxifene, also a SERM, has been studied in breast cancer prevention but not in the treatment of breast cancer and is not approved in Canada for this indication.

Aromatase inhibitors

The enzyme aromatase is found in liver, fat, muscle, and breast tissue and is responsible for most estrogen synthesis in postmenopausal women by conversion of androgenic substrates into estrogen. Aminoglutethimide, an adrenal suppressant, was the original aromatase inhibitor used to treat breast cancer. Aminoglutethimide's toxicity and lack of selectivity prompted the development of modern aromatase inhibitors, which were introduced into clinical trials in the late 1980s. AIs cause marked suppression of plasma estrogen levels in postmenopausal women by inhibition of aromatase. Initial studies compared AIs with megestrol, aminoglutethimide, and tamoxifen in patients with metastatic breast cancer and showed superior efficacy and tolerance, leading to approval for this indication in the 1990s.

AIs are categorized as steroidal (exemestane) and nonsteroidal (anastrozole and letrozole). All are potent inhibitors of aromatase and vary only minimally in their level of estrogen suppression and side-effect profiles. Aromatase inhibitors are significantly more expensive than tamoxifen, costing on average $1800 per year of therapy versus approximately $80 for tamoxifen. Inevitably, cost is a consideration when evaluating province-wide implementation of a new therapy, particularly as significant benefit in overall survival has not yet been widely demonstrated when AIs are compared with tamoxifen. The current review is only of the effects of aromatase in early invasive breast cancer. The use of aromatase inhibitors for noninvasive in situ disease or for primary prevention of breast cancer is not proven and clinical trials are ongoing.

In contrast to tamoxifen, AIs lack partial estrogen agonist activity and are thus not associated with the undesirable increased risks of thromboembolism, gynecological symptoms, and uterine cancer. However, adverse effects of AIs include an increased risk of osteoporosis and osteoporotic fractures, myalgia and arthralgia, and an adverse impact on the lipid profile, all thought to be related to the profound reduction of serum estrogen. Vaginal dryness and decreased libido have been reported. In two separate analyses, no significant differences in overall quality of life were observed between women taking tamoxifen and women taking anastrazole or exemestane.[3,4]

Due to their mode of action, aromatase inhibitors are only effective in postmenopausal women with breast

Table 1. Summary of evidence for therapy with the aromatase inhibitors anastrozole, exemestane, and letrozole for postmenopausal women with ER-positive breast cancer.[8-12, 15]

Aromatase inhibitor	Administration	Benefit
Anastrozole 1 mg/day[8,9] Letrozole 2.5 mg/day[10]	Given for 5 years after diagnosis instead of tamoxifen	• Reduced risk of breast cancer recurrence by approximately 20% • Absolute risk reduction of 3% in clinical trials
Exemestane 25 mg/day[11] Anastrozole 1 mg/day[12]	Given for 2–3 years after 2–3 years of tamoxifen (total duration of hormonal therapy was 5 years)	• Reduced risk of recurrence by approximately 30% - 40% • Absolute risk reduction of 3% - 5% in clinical trials
Letrozole 2.5 mg/day[15]	Given for at least 3–5 years after 5 years of tamoxifen	• Reduced risk of recurrence by 40% and risk of death by 40% in node-positive patients • Absolute risk reduction of 6% in clinical trials

cancer. In premenopausal women, the reduced feedback of estrogen to the hypothalamus and pituitary leads to increased gonadotropin production and an increase in ovarian estrogen production, thereby rendering therapy ineffective and potentially harmful, as ovarian tissue may hypertrophy and uterine bleeding may increase. Many premenopausal women who are treated with chemotherapy become clinically and serologically postmenopausal. The risk of chemotherapy-induced menopause increases with age, and women older than 40 have a greater than 50% risk of being rendered menopausal.[5,6] If menstruation does resume, it usually does so within 12 months, but may not do so for up to 24 months. As AIs are not effective and may be harmful to premenopausal women with breast cancer, they should not be considered until at least 1 to 2 years after chemotherapy-induced menopause.

Evidence of superiority of AIs over tamoxifen

A number of well-designed randomized trials have sought to evaluate the effect of aromatase inhibitors as adjuvant treatment for postmenopausal women with hormone-positive breast cancer. Three strategies have been studied, as follows:

- First-line AI therapy instead of tamoxifen.
- AI therapy after 2 to 3 years of tamoxifen.
- AI therapy at the end of a 5-year course of tamoxifen.

It has not yet been determined which of these three strategies is the optimal algorithm, and no one therapeutic strategy is advocated over another in the 2004 American Society of Clinical Oncology guidelines. However, the role of aromatase inhibitors has been acknowledged with the recommendation that optimal adjuvant hormonal therapy for postmenopausal women with ER-positive breast cancer include an aromatase inhibitor as initial therapy or after treatment with tamoxifen.[7] A summary of the evidence for therapy with AIs is provided in **Table 1**.

First-line AI therapy

In the ATAC (Arimidex, Tamoxifen Alone or in Combination) Trial, the largest randomized adjuvant trial in breast cancer, 9366 postmenopausal women were randomly assigned to 5 years of anastrozole or tamoxifen or a combination of the two.[8,9] After 5.5 years, women treated with anastrozole had a 17% reduction in the relative risk of breast cancer occurrence (disease-free survival) compared with those treated with tamoxifen. This translated into only a 3% absolute improvement in disease-free survival between the anastrozole and tamoxifen groups and there was no difference in risk of death. There was no advantage to combination therapy with anastrozole and tamoxifen over tamoxifen alone.

In a second large adjuvant trial (BIG 1-98), first-line therapy with letrozole was compared with tamoxifen and found similar results.[10] With a shorter follow-up time there was a 19% difference in disease-free survival between the two groups, but overall survival was not significantly different. With longer follow-up, a reduction in mortality may be observed in both of these trials as women with recurrent breast cancer have a significantly shortened life expectancy.

Trials of AIs after 2 to 3 years of tamoxifen

Shortly after the results of first-line AI therapy were reported, the results of a second strategy to incorporate an aromatase inhibitor into adjuvant therapy were released. In this case, tamoxifen was prescribed as initial therapy and an AI was substituted after 2 to 3 years to complete a total of 5 years of hormonal therapy.

There are several potential advantages to this strategy. First, women are exposed to two treatments with differing mechanisms of action. Second, the inherent risk of AI therapy, including osteoporosis, may be reduced by a shorter duration of exposure and the prior use of tamoxifen. Third, the cumulative risks of tamoxifen therapy, including uterine malignancy and

thrombosis, are also limited by a shortened duration of tamoxifen therapy.

In the International Exemestane Study (IES), women who had received 2 to 3 years of tamoxifen were randomly assigned to receive exemestane or to continue on tamoxifen to complete 5 years of adjuvant hormonal therapy.[11] At a median follow-up of 31 months, women who switched to exemestane had a 32% reduction in the risk of recurrence, and a corresponding 5% absolute improvement in disease-free survival at 3 years. There was no difference in overall survival but a trend was reported.

In a second, smaller trial, postmenopausal women were switched to anastrozole after 2 years of adjuvant tamoxifen, resulting in a 40% relative risk reduction and 3% absolute risk reduction.[12]

Trial of letrozole after 5 years of tamoxifen

Previous evidence suggested that 5 years of adjuvant hormonal therapy provides optimal benefit, with a longer duration of tamoxifen use possibly associated with worse survival outcomes.[13] Yet, half of breast cancer relapses occur later than 5 years after diagnosis.[1,2,14] In the NCIC MA17 trial, the benefit of letrozole after 5 years of tamoxifen was evaluated. Women who were cancer-free after taking 5 years of tamoxifen were treated with an intended 5 years of letrozole versus placebo.[15] After only 2.4 years follow-up there was a 40% decrease in breast cancer occurrence in women treated with letrozole, which translated into a benefit of 6% in absolute terms. In patients with node-positive breast cancer there was also a 40% reduction in risk of death, making this the first of the AI trials to show a survival benefit.

Other uses of AIs

Outside the realm of oncology, AIs have been used for treatment of severe endometriosis. In a randomized trial of anastrozole plus goserelin (a gonadotropin-releasing hormone analog, also known as a luteinizing-hormone-releasing hormone or LHRH) versus goserelin alone, AI use resulted in a significant reduction in recurrent pain.[16] AIs have also been used for ovarian stimulation for women undergoing in vitro fertilization. It should be noted, however, that when aromatase inhibitors are used for these indications, they are not paid for by the BCCA.

Side effects of AIs versus tamoxifen

In the trials referred to here, hot flushes were commonly reported (40% to 60%) and occurred with similar frequency in women taking AIs or tamoxifen.[8,11,15] In the MA 17 trial, even women who were on no hormonal treatment after 5 years of tamoxifen had a 54% incidence of low-grade hot flushes. A reduction in gynecological side effects (such as vaginal discharge or bleeding) with aromatase inhibitors was most notable when an AI rather than tamoxifen was used as first-line therapy. Rates of vaginal bleeding (5% versus 10%) and hysterectomy (1% versus 5%) were both significantly less with anastrozole than tamoxifen.[9] The difference in gynecological side effects between tamoxifen and AIs are less apparent after 2 years of tamoxifen use, as tamoxifen-induced gynecological symptoms predominate in the initial years of therapy. Although low in both groups, a reduction in the thromboembolic events and risk of uterine cancer was observed with AIs versus tamoxifen.

Regarding other side effects, 5 years of anastrozole use was associated with a 3% absolute increase in osteoporotic fractures,[9] whereas 2 to 3 years of AI therapy after tamoxifen was associated with a 1% absolute increase in osteoporotic fractures and a 2% absolute increase in osteoporosis.[5,11] An adverse effect on lipid profile was observed in one trial with letrozole, and in two trials there was a questionable trend of increased serious cardiovascular events.[9,10] The extent and significance of cardiovascular risk associated with AIs is being investigated.

Risk of recurrence with tamoxifen use

Two recent studies of the BCCA Breast Cancer Outcomes Database have sought to estimate risk of recurrence of breast cancer in postmenopausal women treated with tamoxifen.[17,18] In the first study, the risk of early recurrence of breast cancer was determined among postmenopausal women in British Columbia treated with tamoxifen alone or in addition to chemotherapy for breast cancer. Early recurrence was defined as relapse occurring within 2.5 years of initial diagnosis with breast cancer. Results indicate that women who have more than three nodes positive, or who have high-grade breast cancer (grade 3) or low ER-positive (1+) breast cancer are at significantly greater risk of recurrence within the first 2.5 years after diagnosis[17]

While it is not yet known if first-line treatment with AIs will reduce the risk of death from breast cancer, current BCCA guidelines recommend that women at high risk of early recurrence and no contraindications to AIs be treated with an AI instead of tamoxifen. For postmenopausal women who do not meet these criteria, BCCA recommends initial therapy with tamoxifen followed by a switch to an AI after 2 to 5 years.

Table 2. Risk of breast cancer death and breast cancer occurrence 6 to 10 years after diagnosis if disease-free after 5 years of tamoxifen.

Nodal involvement and tumor size	Number of patients	Risk of breast cancer death between years 6 and 10 (%)	Risk of breast cancer occurrence between years 6 and 10* (%)
Node-negative, all grades	418	4	10
Node-negative, grade 1	42	0	3
1–3 nodes positive	380	9	15
4–9 nodes positive	109	22	30

* Defined as cancer recurrence or second primary breast cancer

In an attempt to estimate the risk of late breast cancer relapse, breast cancer event rate and mortality were determined in postmenopausal women treated in British Columbia with 5 years of tamoxifen.[18] Risk of breast cancer events (defined as recurrence and second breast cancers) and mortality are provided in **Table 2**.

In this study, nodal involvement was the most important predictor of breast cancer events or death after 5 years of tamoxifen. Women with 1 to 3 nodes positive had a 15% risk, and women with 4 to 9 nodes positive had a 30% risk of breast cancer occurrence. Women who had low-grade node-negative disease had a very low risk (3%) of breast cancer occurrence after 5 years of tamoxifen. Current BCCA guidelines recommend that women with node-positive or with high-grade node-negative breast cancer be considered for another 3 to 5 years of therapy with letrozole after 5 years of tamoxifen. Women with low-grade node-negative breast cancer should not routinely receive letrozole after 5 years of tamoxifen, since the overall risk of recurrence is very low.

Guidelines for AI use

Aromatase inhibitors represent a new standard of care for many postmenopausal women receiving adjuvant hormonal therapy for early breast cancer. There are three different AIs and three different strategies to incorporate AIs into adjuvant therapy. The question of which strategy is superior in terms of efficacy and side effects has not yet been answered.

For postmenopausal women with breast cancer who are at high risk of early relapse, first-line therapy with 5 years of AIs is recommended. Women are considered at high risk if they have more than three nodes positive, have high-grade disease (grade 3), or low ER-positive (1+) disease. Otherwise, first-line therapy with tamoxifen for 2 to 3 years remains the standard. After 2 to 3 years of tamoxifen, physicians are asked to consider switching women to AI therapy for 2 to 3 years to complete a total of 5 years of hormonal treatment. It is recommended that women who have already received more than 3 years of tamoxifen continue on tamoxifen for a total of 5 years, after which they should consider the option of 3 to 5 more years of AI therapy. Women with initially node-positive breast cancer or high-grade node-negative breast cancer and a reasonable 5-year life expectancy should be considered for 3 to 5 years of AI therapy.

Patients with node-negative and low-grade disease (grade 1) have a favorable prognosis[18,19] and are generally adequately treated with 5 years of tamoxifen alone and no AI therapy. Low-grade breast cancer accounts for approximately 16% of all breast cancer.[2]

For premenopausal women with ER-positive breast cancer, tamoxifen remains the standard therapy. These patients are not candidates for aromatase inhibitor therapy. For women who become menopausal after chemotherapy and remain so for 1 to 2 years, a switch to an AI may be optimal. There is not yet any evidence for the use of an LHRH agonist such as goserelin with an AI.

It is recommended that physicians assess a woman's risk of osteoporosis when considering AI therapy. If there are any risk factors for osteoporosis, a baseline bone density test should be performed.[20] AIs may also have an adverse effect on lipid profile and there is a possible but not yet quantified cardiovascular risk. A baseline lipid profile should be performed at the time of initiating AI therapy.

The recommendations described here will be updated as the results of new trials become available and current trials continue. For now, BCCA recommends the exclusive use of first-line AI therapy for some postmenopausal women and the sequential use of tamoxifen followed by an AI for most postmenopausal women with early stage hormone-positive breast cancer. The BCCA does not recommend the use of AI therapy for premenopausal women with breast cancer.

Full guidelines
The full guidelines can be viewed at www.bccancer.bc.ca.

Competing interests

In the last 5 years Dr Kennecke has received fees for speaking and fees from consultancy from AstraZeneca, Novartis, and Pfizer.

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