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Endocrine Therapy for Breast Cancer

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Breast cancer is the most common type of cancer in women. There is an estimated average lifetime risk of 12.5% for women without additional risk factors.[1] The risk is even higher in women with risk factors. Women with mutations in the *BRCA* tumor suppressor genes can have an estimated lifetime risk up to 85%,[1] and approximately 33% of patients with a history of ductal carcinoma in situ (DCIS; a non-invasive carcinoma contained within the duct) develop invasive disease within 20 years.[2] This article reviews risk factors and evaluates treatments for prevention of breast cancer. Typical therapy for primary chemoprevention consists of an aromatase inhibitor or selective estrogen receptor modulator (SERM). Endocrine therapy is also used as adjuvant treatment in women with a history of breast cancer after surgery, radiation or chemotherapy and for treatment of metastatic disease. Table 1 describes place in therapy for preventative breast cancer therapies.

Table 1. Preventative Breast Cancer Therapies[3-6]

Drug	Class	Place in Therapy
Anastrozole	Aromatase Inhibitors	- Adjuvant treatment of hormone receptor-positive or advanced breast cancer - Use in postmenopausal women - Off-label: primary chemoprevention and use in premenopausal women*
Exemestane		
Letrozole		- Adjuvant therapy for hormone receptor-positive, advanced or metastatic cancer - Use in postmenopausal women - Off-label: Use in premenopausal women*
Raloxifene	Selective Estrogen Receptor Modulators (SERMs)	- Primary chemoprevention - Treatment or prophylaxis of postmenopausal osteoporosis - Use in postmenopausal women
Tamoxifen		- Primary chemoprevention - Adjuvant treatment of DCIS and hormone receptor-positive, advanced, or metastatic breast cancer - Use in pre- and post-menopausal women
Toremifene		- Metastatic breast cancer in postmenopausal women

*Use of an aromatase inhibitor in premenopausal women requires concurrent ovarian suppression or ablation.

Breast Cancer Risk

National Comprehensive Care Network (NCCN) and American Society of Clinical Oncology guidelines recommend consideration of chemoprevention or surgical risk reduction in women at least 35 years of age with a life expectancy greater than 10 years who are at high risk of breast cancer and little risk of complications from therapy.[5] High risk is defined as women with a 5-year risk greater than 1.7%, exposure to thoracic radiation before the age of 30 years, or those with a history of lobular carcinoma in situ.[5] Risk can be estimated using the modified Gail model (http://www.cancer.gov/bcrisktool). This risk assessment tool accounts for multiple risk factors including age, ethnicity, reproductive history (including early menarche and older age at menopause or live birth), family history, and positive history of atypical hyperplasia.[7] The tool is typically not used for populations with prior history of carcinoma in situ or *BRCA* mutations as these factors are very strong predictors of invasive breast cancer.[7] Additional treatment options such as surgery or radiation should be considered in populations who have high risk for breast cancer.

Primary Chemoprevention

Both tamoxifen and raloxifene are FDA approved for primary prevention of breast cancer. Exemestane and anastrozole may be used off-label for chemoprevention, but are more commonly used as adjuvant treatment in women with a history of breast cancer. A systematic review conducted by the U.S. Preventative Services Task Force in 2013 compared tamoxifen and raloxifene for primary prevention of breast cancer in high-risk women.[8] Median duration of treatment ranged from 3-5 years with follow-up from 7-13 years.[8] In placebo-controlled trials, both tamoxifen (relative risk [RR] 0.70, 95% CI 0.59 to 0.82; 7 cases per 1000 over 5 years; number needed to treat [NNT] 143) and raloxifene (RR 0.44, 95% CI 0.27 to 0.71; 9 cases per 1000 over 5 years; NNT 111) reduced the incidence of invasive breast cancer but had no impact on non-invasive breast cancer or estrogen receptor-negative breast cancer.[8] Upon direct comparison in a randomized controlled trial (RCT; n=19,747), raloxifene had a higher incidence of invasive breast cancer (RR 1.24, 95% CI 1.05 to 1.47; 5 cases per 1000 over 5 years).[8] No difference was observed for either agent in all-cause mortality or mortality due to cancer. Though they are not approved by the FDA for primary prevention, therapy with either anastrozole or exemestane for 5 years has also shown to significantly reduce risk for breast cancer recurrence compared to placebo (RR 0.468, 95% CI 0.346 to 0.634; p<0.001; NNT 61).[9]

Secondary Prevention

After primary treatment with surgery, chemotherapy, or radiation, adjuvant treatment for 5 to 10 years with an aromatase inhibitors or tamoxifen can prevent recurrence and improve survival. Choice of therapy depends on type of cancer and menopause status at time of cancer diagnosis.

Following initial treatment of DCIS, both tamoxifen and anastrozole may be considered in pre- and post-menopausal women to reduce breast cancer recurrence.[5] In a systematic review including 2 RCTs (n=3,375), tamoxifen decreased recurrence of ipsilateral DCIS (RR 0.75 95% CI 0.61 to 0.92), contralateral DCIS (RR 0.50 95% CI 0.28 to 0.87), and contralateral invasive cancer (RR 0.57 95% CI 0.39 to 0.83).[10] A statistically significant reduction was not shown for invasive ipsilateral carcinoma (HR 0.79, 95% CI 0.62 to 1.01) or all-cause mortality.[10] One recent RCT of anastrozole (n=2,980) also demonstrated similar rates of breast cancer recurrence compared to tamoxifen (HR 0.89, 95% CI 0.64 to 1.23) with no difference in mortality.[11]

For treatment of invasive breast cancer, tamoxifen or an aromatase inhibitor may be considered in premenopausal women.[6] Aromatase inhibitors alone are unable to prevent production of estrogen from the ovaries, and use in premenopausal women requires concurrent ovarian suppression or ablation.[6] In postmenopausal women, NCCN recommends the following regimens:

- Tamoxifen for 5-10 years (if unable to use an aromatase inhibitor)[6] OR
- Aromatase inhibitor for 5 years[6] OR
- Sequential therapy with tamoxifen for 2-3 years followed by an aromatase inhibitor for up to 5 years[6] OR
- Sequential therapy with an aromatase inhibitor for 2-3 years followed by tamoxifen for 5 years total[6] OR
- Tamoxifen for 4.5-6 years followed by 5 years of an aromatase inhibitor[6]

One systematic review (n=31,920) compared efficacy of aromatase inhibitors versus tamoxifen for treatment of estrogen receptor-positive early breast cancer.[12] Compared to 5 years of tamoxifen, use of an aromatase inhibitor for 5 years was associated with reduced risk of breast cancer recurrence (10-year absolute risk reduction [ARR] 3.6%, 95% CI 1.7 to 5.4%; p<0.00001) and all-cause mortality (ARR 2.7%; RR 0.89, 95% CI 0.81 to 0.97; p=0.01).[12] Similarly, at 10 years, patients on tamoxifen for 2-3 years followed by an aromatase inhibitor for a total of 5 years had a lower risk of breast cancer recurrence (ARR 2.0%, 95% CI 0.2 to 3.8; p=0.0001), breast cancer mortality (ARR 1.5%, RR 0.84, 95% CI 0.72 to 0.96; p=0.01), and all-cause mortality (ARR 2.9%, RR 0.82, 95% CI 0.73 to 0.91; p=0.0002)

compared to 5 years of tamoxifen.[12] Because aromatase inhibitors improve survival and reduce disease recurrence, NCCN guidelines recommend tamoxifen monotherapy only in women who remain premenopausal for the duration of their treatment or those unable to tolerate aromatase inhibitors.[6]

Total treatment duration is typically 5 to 10 years following primary treatment. Evidence from 1 systematic review suggests that extending therapy to 10 years improves breast cancer survival (OR 0.87; 95% CI 0.81 to 0.95; p=0.001) and relapse-free survival (OR 0.79; 95% CI 0.68 to 0.92; p=0.002) compared to 5 years of therapy.[13] However, other systematic reviews have found no difference in all-cause mortality in patients receiving 10 or 5 years of therapy.[14,15] In addition, evidence for use of an aromatase inhibitor beyond 5 years is limited. One RCT (n=1,918) has examined letrozole versus placebo as extended therapy for 5 years following completion of an initial 4.5 to 6 years of an aromatase inhibitor. This trial demonstrated reduced rates of disease-free survival and breast cancer recurrence (HR 0.66, 95% CI 0.48 to 0.91).[16] Nonetheless, due to limited evidence, current standard of care for aromatase inhibitor use is a maximum of 5 years alone or in combination with tamoxifen.

Safety of Endocrine Therapy

Risks and benefits of treatment must be weighed carefully especially when used in the risk reduction setting (women with DCIS or at high risk of breast cancer). In women with a history of invasive cancer, benefits of therapy generally outweigh the risks. The results of several high quality systematic reviews examining the safety of these agents are summarized here.

Endometrial Cancer – Tamoxifen is consistently associated with a higher risk of endometrial cancer compared to other treatments. When compared directly to tamoxifen, raloxifene had 5 fewer cases of endometrial cancer per 1000 women (RR 0.55, 95% CI 0.36 to 0.83).[8] Aromatase inhibitors also demonstrated a significantly decreased risk compared to tamoxifen (10-year ARR 0.8%; RR 0.33, 95% CI 0.21 to 0.51; p<0.0001).[12] Risk of cancer in women taking tamoxifen also increases with age. Compared to placebo, women over 50 years of age had a significant increased risk for endometrial cancer (RR 3.32, 95% CI 1.95 to 5.67; p<0.0001), but no difference was seen in women less than 50 years of age (RR 1.19, 95% CI 0.53 to 2.65; p=0.60).[17]

Thromboembolic Events – Risk of venous thromboembolic events (VTE) is increased with both tamoxifen (RR 1.93, 95% CI 1.41 to 2.64; 4 cases in 1000 women) and raloxifene (RR 1.60, 95% CI 1.15 to 2.23; 7 cases in 1000 women) compared to placebo.[8] Upon direct comparison to tamoxifen, raloxifene had lower risk of VTE (RR 0.75, 95% CI 0.60 to 0.93; 4 cases in 1000 women).[8] Compared to placebo, rates of pulmonary embolism (PE) were significantly increased with tamoxifen (RR 2.69, 95% CI 1.12 to 6.47), but failed to reach statistical significance with raloxifene (RR 2.19, 95% CI 0.97–4.97).[8] Raloxifene was also associated with a higher stroke mortality compared to placebo (RR 1.49, 95% CI 1.00 to 2.24).[8] Compared to tamoxifen, aromatase inhibitors demonstrated decreased odds of VTE (ARR 1.3%; OR 0.55, 95% CI 0.46 to 0.64; p<0.001).[18]

Ocular Effects – In a systematic review of primary prevention trials, rate of cataracts was higher in tamoxifen users than in those taking raloxifene (RR 0.80, 95% CI 0.72 to 0.95; 15 cases per 1000 women).[8]

Fractures and Musculoskeletal Effects – Tamoxifen and raloxifene are typically associated with decreased rates of fractures. In postmenopausal women, these SERMs act as estrogen agonists in bone tissue and can help prevent osteoporosis. In a systematic review of primary prevention RCTs, rates of vertebral fractures were reduced with raloxifene (RR 0.61, 95% CI 0.54 to 0.69; 7 cases in 1000 women), non-vertebral fractures were reduced with tamoxifen (RR 0.66, 95% CI 0.45 to 0.98; 3 cases in 1000 women), and rates of vertebral fractures were similar with direct comparison of the agents.[8] Compared to tamoxifen, aromatase inhibitors were associated with a 2.7% increased risk of fractures at 5 years (RR 1.42 95% 1.28 to 1.57; p<0.0001), and risk remained elevated in the 5 years after treatment discontinuation (RR 1.29, 95% 1.09 to 1.53; p=0.003).[12] Other adverse effects commonly associated with aromatase inhibitors include arthralgias and myalgias.[3,4] Because adherence to endocrine therapy is often poor, with reported non-adherence rates of 10.8% to 85%,[19] these adverse effects must be considered carefully as they may be limiting factors to treatment.

Conclusions

As primary chemoprevention, use of endocrine therapy decreases incidence of breast cancer without any effect on mortality. Compared to raloxifene upon long-term follow up, tamoxifen was associated with lower rates of recurrent breast cancer. However, tamoxifen is also associated with increased rates of endometrial cancer, thrombotic events, and cataracts. When used as primary chemoprevention, the risks and benefits of therapy must be weighed carefully. As adjuvant treatment of invasive breast cancer, aromatase inhibitors have demonstrated reduced disease recurrence and mortality compared to tamoxifen. More information on these treatment options, along with other therapeutic reviews, can be found on the Oregon Health Plan fee-for-service searchable preferred drug list at http://www.orpdl.org/drugs/.

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