Adjuvant Endocrine Therapy

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Background

Adjuvant endocrine therapy is a mainstay of treatment for women with hormone-receptor (estrogen-receptor and/or progesterone-receptor) expressing breast cancers. Extensive clinical trials over decades have demonstrated compelling improvements in overall survival and disease-free survival with use of adjuvant endocrine therapy. Along with implementation of widespread screening mammography programs, use of adjuvant endocrine therapy has contributed substantially to the decline in breast cancer mortality seen in the US and other developed societies. Around the world, it is likely that adjuvant endocrine treatment has contributed more to the reduction in cancer mortality than any other therapy employed in medical oncology.

Available adjuvant endocrine options include selective estrogen-receptor modulators such as tamoxifen, which is effective in women regardless of menopausal status. For postmenopausal women, aromatase inhibitors have emerged as treatment options either in sequential addition to or instead of tamoxifen. For premenopausal patients, ovarian suppression or ablation is also an effective therapy. Important questions in clinical application of adjuvant endocrine treatment include the duration of therapy, the role of ovarian suppression in younger women also given tamoxifen, and the enduring role for tamoxifen in the management of postmenopausal patients. In addition, there are persistent challenges in management of the unique side effects of adjuvant endocrine therapy, including menopausal symptoms and considerations of bone and musculoskeletal health. Because of the well-tolerated nature of these agents, and because of their efficacy in preventing breast cancer recurrence, regular assessment of patient symptoms and treatment compliance are important for assuring optimal long-term treatment results.

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F.M. Dirbas and C.E.H. Scott-Conner (eds.), *Breast Surgical Techniques and Interdisciplinary Management*, DOI 10.1007/978-1-4419-6076-4_62,

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Tamoxifen

Tamoxifen has historically been the treatment standard for adjuvant endocrine therapy. The Early Breast Cancer Trialists' Collaborative Group overview analysis demonstrates that 5 years of adjuvant tamoxifen lowers the risk of cancer recurrence by 41% and reduces risk of breast cancer death by 34% (1). These gains are durable and persist through at least 15 years of follow-up. Similar gains in risk reduction and overall survival are seen irrespective of patient age or menopausal status. Shorter treatment durations of less than 5 years yield lower gains in risk reduction than 5 years of therapy. Initial prospective trials of extended duration tamoxifen treatment beyond 5 years did not suggest clinical improvement (2). For this reason, 5 years of tamoxifen has been considered the routine treatment duration, and that treatment plan has been the "standard" arm in many recent trials of adjuvant endocrine therapy. Recently, larger randomized trials have explored continuation of tamoxifen beyond 5 years and demonstrated modest additional risk reduction with longer treatment (3, 4). The full clinical significance of longer tamoxifen treatment and associated side effects remain unclear but are of ongoing interest, particularly in premenopausal women, in whom aromatase inhibitor therapy is contraindicated, or in women without access to AIs or who cannot tolerate AI therapy.

Tamoxifen is effective in ER-positive breast cancers, but not in ER-negative tumors (5). Aside from ER status, predictors of tumor sensitivity or resistance to tamoxifen are not well established. ER-positive tumors that express the HER2/neu oncogene (i.e., HER2 positive) carry a greater risk of recurrence than HER2-negative tumors; however, endocrine therapy with tamoxifen or tamoxifen plus ovarian suppression can be effective among such tumors (6). The 21-gene recurrence score assay has been shown to be a prognostic assay for outcomes in patients with ER-positive, node-negative tumors receiving tamoxifen, but does not fully discriminate cases where tamoxifen should not be administered (7). Tamoxifen achieves equivalent relative risk reduction in patients given chemotherapy or not, though when adjuvant chemotherapy is given, it should be delivered before initiation of tamoxifen both to improve efficacy and reduce the risk of treatment complications (8, 9).

The side effects of tamoxifen are well characterized and include common menopausal symptoms such as hot flashes and night sweats. Tamoxifen can rarely be associated with increased risk of thromboembolic events such as deep venous thrombosis, and with uterine cancer. These risks are small in absolute terms (risk less than 1%), appear less common among premenopausal than postmenopausal patients, and are related in part to duration of therapy (10).

Tamoxifen is metabolized by cytochrome P450 into active metabolites including endoxifen. Recently, there have been data suggesting that pharmacogenomic variation in tamoxifen metabolism arising from genetic variation in the CYP2D6 allele may contribute to significant variation in endoxifen levels (11, 12). Concurrent use of P450 inhibitors including some serotonin-selective reuptake inhibitors including fluoxetine and paroxetine may also affect tamoxifen metabolism (13). The clinical significance of these finding remains ill-defined, and genetic testing for CYP2D6 or other allelic variations are not yet well established. Patients on tamoxifen should probably avoid concurrent use of known P450 inhibitors.

Adjuvant Endocrine Therapy in Premenopausal Women

Adjuvant endocrine treatment is essential for premenopausal women with ER+ breast cancer (14, 15). Historically, young women have had worse outcomes with early-stage breast cancer. It is likely that age is a surrogate marker for a variety of adverse biological factors more commonly found in younger women. These include lower levels of expression of hormone receptors, or lack of hormone receptor expression, higher tumor grade, more likely overexpression of HER2, and higher rates of tumor proliferation or lymphovascular invasion. Nonetheless, endocrine therapy is effective in younger women, and part of the adverse outcomes ascribed to younger women arise from data generated in an era prior to use of adjuvant endocrine treatment (16). Tamoxifen is effective in younger women, irrespective of patient age or menopausal status, and is the standard endocrine treatment for younger women (1, 17).

The principal controversy in management of premenopausal women with ER+ breast cancer is the role of ovarian suppression. Clinical trials have demonstrated that ovarian suppression affords lower risk of recurrence compared to no adjuvant treatment (18). In addition, older trials comparing ovarian suppression with adjuvant chemotherapy – typically CMF-based chemotherapy – demonstrated rough equivalence between these treatment options (15, 19). In modern practice, however, the question remains unanswered as the fundamental problem – knowing whether ovarian suppression adds to clinical outcomes among women given tamoxifen with or without chemotherapy. This awaits data from prospective clinical trials. The question is further complicated by the impact of chemotherapy-induced amenorrhea. The high rate of chemotherapy-associated menopause among premenopausal women, particularly women aged 40 and older, has confounded trials designed to analyze the impact of ovarian suppression in women also receiving chemotherapy.

Attempts have been made to sort out whether ovarian suppression might add to chemotherapy and/or tamoxifen treatment. An overview of gonadotropin releasing hormone (GnRH) agonist therapy treatment in premenopausal breast cancer suggested a nonsignificant 15% risk reduction with use of ovarian suppression and tamoxifen compared to tamoxifen alone (20). A randomized trial comparing chemotherapy vs. chemotherapy plus GnRH agonist vs. the combination and tamoxifen demonstrated an advantage for the addition of tamoxifen in the overall patient population (21). For women under age 40, who were less likely to undergo chemotherapy-induced amenorrhea, the sequential addition of GnRH agonist and then tamoxifen yielded stepwise improvement in outcome. The onset of chemotherapy-induced amenorrhea has been studied as a prognostic factor in premenopausal breast cancer. The vast majority of studies suggest that women with ER+ tumors experiencing chemotherapy-related amenorrhea have a better long-term prognosis than women not experiencing menopause (22). In one of the few trials that included tamoxifen treatment, women with chemotherapy-induced menopause had better outcomes either with or without the addition of tamoxifen (23). Collectively, these experiences suggest that the induction of ovarian suppression might improve on outcomes in patients also receiving tamoxifen treatment, but the true significance and magnitude of such benefit remains unclear. Women receiving ovarian suppression and tamoxifen are likely to experience more profound side effects than women receiving tamoxifen alone, including greater urogenital discomfort, sexual dysfunction, menopausal symptoms, and bone demineralization.

Aromatase inhibitors are contraindicated in premenopausal women, as residual ovarian physiological function can upregulate aromatase enzyme expression and overcome the effects of AI treatment. Case reports have documented late recovery of ovarian function in women with chemotherapy-induced amenorrhea while on AI therapy (24, 25). These cases are reminders that tamoxifen remains the treatment of choice for women in which there is any question of residual ovarian function and in women premenopausal at time of diagnosis. The role of AIs in premenopausal women given concurrent ovarian suppression is under active investigation. The TEXT trial compares ovarian suppression with tamoxifen against ovarian suppression with an aromatase inhibitor. ABCSG trial 12 was a randomized study directly comparing ovarian suppression with tamoxifen or an AI, and preliminary data suggest no differences in outcome with either of those two agents (26).

In summary, premenopausal women with ER+ breast cancer should receive adjuvant tamoxifen. These women may also wish to consider ovarian suppression, though the gains are hard to quantify at present, and ovarian suppression is likely to be associated with greater side effects. The SOFT trial, a randomized study of tamoxifen with or without ovarian suppression, will hopefully define with clarity the role of ovarian suppression in young women.

Adjuvant Endocrine Therapy in Postmenopausal Women

While 5 years of tamoxifen has been the traditional treatment for postmenopausal women with ER+ early-stage breast cancer, multiple recent trials have suggested that incorporation of aromatase inhibitors into the treatment program can lower the risk of tumor recurrence (27). Aromatase inhibitors suppress the conversion of androgens into estrogens in postmenopausal women, achieving profound estrogen deprivation. The treatment benefits and side effects of AI therapy are consequences of the hypoestrogenemic state achieved by these drugs. Commercially available aromatase inhibitors include nonsteroidal, reversible inhibitors such as anastrozole and letrozole, and the steroidal, irreversible agent exemestane. All three of these agents achieve generally comparable levels of estrogen suppression. Each has been studied in different sets of populations, and there are no meaningful data comparing efficacy of one or the other agent in the adjuvant setting. It is likely that the reported data represent a “class effect” of these drugs. Anecdotal experience suggests that some patients will tolerate one product better than another, for unclear reasons. Previous generations of aromatase inhibitors, including the agent aminoglutethimide, were less selective in their targeting of the aromatase enzyme and were associated with far greater symptoms related to steroid insufficiency and rash. Such agents are of historical interest only at this time.

The major adjuvant trials of aromatase inhibitor therapy all compared treatment plans that incorporated AIs against 5 years of tamoxifen therapy, the traditional treatment standard. These trials are summarized in Table 62.1. AI therapy was evaluated in three different clinical contexts – as upfront (or primary) treatment of newly diagnosed postmenopausal breast cancer, as sequential (or switching) therapy after 2 or 3 years of tamoxifen treatment, and as extended adjuvant therapy after 5 years of tamoxifen. In each instance, the utilization of an AI led to a lower risk of tumor recurrence than 5 years of tamoxifen alone.

The risk reduction seen in each trial is shown in Table 62.1. Upfront use of an AI lowers risk of recurrence by 10–20% compared to 5 years of tamoxifen, sequential therapy of tamoxifen followed by an AI for a total of 5 years by 24–40% compared to 5 years of tamoxifen, and extended AI therapy by 30–40% compared to stopping after 5 years of tamoxifen. Because of the generally favorable prognosis of patients in these various treatment trials, the absolute gains associated with these reductions in risk of recurrence translate to differences on the order of 3–10% through about 5 years of follow-up. To date, the only studies that have demonstrated a survival advantage for incorporation of AI therapy into adjuvant treatment have been the "switching" trials of sequential therapy. The lack of a survival difference is likely due to many factors, including the modest relative and absolute risk reduction seen with AI therapy, the limited available follow-up, the generally favorable prognosis of ER+ postmenopausal breast cancer, the substantial fraction of disease-related events that are nonlethal ipsilateral recurrences or contralateral breast cancers (28), and competing causes of mortality in older patients.

Formal quality of life analyses have shown similar – and modest – effects of either tamoxifen or aromatase inhibitors on health-related quality of life and daily function (29, 30). Tamoxifen and aromatase inhibitors do differ in their common side effect profiles. While both agents can be associated with hot flashes and night sweats, AI therapy is associated with greater vaginal dryness and sexual dysfunction including loss of libido. Aromatase inhibitors lack the rare risks of endometrial cancer and thromboembolism seen with tamoxifen and are associated with a lower incidence of gynecological bleeding and of hysterectomy. Because of their estrogen deprivation implications, AI therapy is associated with accelerated osteopenia, osteoporosis, and osteoporotic fractures compared to tamoxifen treatment (31, 32). AI-associated osteoporosis can be mitigated with use of bisphosphonate therapy (33). Patients on AIs should be screened regularly for bone mineral density and initiate treatment with standard interventions such as calcium and vitamin D supplementation, weight-bearing exercise, and bisphosphonates according to established guidelines (34). Aromatase inhibitors are also associated with an arthralgia syndrome, characterized by achiness or stiffness in the joints (especially of the hands, arms, knees, and feet) (35). The true prevalence of this condition is not known, though emerging data suggest it is a very common syndrome, tends to abate over long periods of time, and contributes to discontinuation of AI therapy in a subset of patients (36).

Despite the wealth of data on adjuvant treatment with aromatase inhibitors, important practical questions remain that await results from ongoing clinical trials. So far, neither patient clinical factors nor tumor biomarkers have been defined that clearly suggest which initial treatment strategy would be optimal for a given patient or cancer. Neither quantitative measures of ER or PR nor tumor HER2 status appears to define patients best suited for one treatment plan or agent, or another (37). In the BIG 1-98 trial, tumors with low Ki67 proliferation indices appeared to respond equally well to either tamoxifen or an AI, while those with high Ki67 measures selectively benefited from AI therapy (38), but this observation awaits confirmation.

A consequence of the design of the major adjuvant trials is that neither the total duration of adjuvant endocrine therapy nor the duration of AI treatment is well established. For patients receiving upfront AI treatment, safety and efficacy data exist for 5 years of AI treatment. For patients begun on tamoxifen, there are data for 2–3 years of AI or of 5 years

Table 62.1 Major randomized trials of aromatase inhibitor therapy in postmenopausal, early-stage breast cancer

Trial	References	Eligibility	Treatment arms	Number of patients; DFS hazard ratio
Up-front/primary therapy				
ATAC	(1, 2)	Newly diagnosed	T × 5 A × 5 T + A × 5	9,366; HR 0.87
BIG 1-98	(3, 4)	Newly diagnosed	T × 5 L × 5 T × 2 → L × 3 L × 2 → T × 3	8,028; HR 0.82
Sequential/switching therapy				
ABCSG 8	(5)	Newly diagnosed	T × 5 T × 2 → A × 3	2,926; HR 0.76
ARNO 95		Disease-free after 2 years T	T × 3 A × 3	979; HR 0.66
IES	(6, 7)	Disease-free after 2–3 years T	T × 2–3 years E × 2–3 years	4,724; HR 0.76
ITA	(8)	Disease-free after 2–3 years T	T × 2–3 years A × 2–3 years	448; HR 0.57
Extended therapy				
MA17	(9, 10)	Disease-free after 5 years T	Placebo L × 5 years	5,187; HR 0.58
NSABP B-33	(11)	Disease-free after 5 years T	Placebo E × 5	1,598; HR 0.68
ABCSG 6a	(12)	Disease-free after 5 years T ± aminoglutethimide	No treatment A × 3 years	856; HR 0.64

T tamoxifen; *A* anastrozole; *E* exemestane; *L* letrozole

of AI use, yielding different total durations of therapy (either 5 or 10 years), depending on the length of initial tamoxifen exposure. These vagaries will not be readily resolved by existing treatment studies. The growing appreciation for the long natural history of ER+ breast cancer in postmenopausal women is prompting longer durations of adjuvant therapy. At the moment, however, data only exist in support of 5 years of initial AI treatment. For women beginning with tamoxifen, it seems reasonable, based on the available safety experience, to offer 5 years of AI therapy after their initial years of tamoxifen treatment; the best total duration of such therapy is not known.

Finally, it remains unclear which initial treatment choice – tamoxifen or an AI – would yield optimal long-term tumor control. Recent data from the BIG 1-98 and TEAM trials, which compared initial use of an AI vs a sequential treatment program of tamoxifen followed by an AI, show identical rates of tumor recurrence with either strategy (41, 42). Thus, either of these treatments plans is a valid option for postmenopausal women. Modeling studies suggest that a crossover strategy built around sequential therapy might offer superior long-term tumor control (39), but these computer simulations await clinical confirmation. At present, clinical judgment factoring in patient characteristics, preexisting health conditions, and desired side effect profiles informs the selection of initial therapy. Expert panel guidelines from the American Society of Clinical Oncology (40), the St. Gallen Consensus Conference on Early Stage Breast Cancer (17), and the National Comprehensive Cancer Network (available at www.nccn.org) endorse either upfront use of an AI or tamoxifen as initial treatment and recommend incorporation of an AI at some point during adjuvant endocrine therapy for postmenopausal women.

Conclusions

Despite decades of clinical research, important questions remain about the optimal treatment strategies for women with ER+ breast cancers. Nonetheless, it is clear that multiple years of antiestrogen treatment with tamoxifen or aromatase inhibitors is a critical intervention. Familiarity with the common side effects of these drugs can help clinicians and patients to be more understanding and more compliant with these medicines. Emerging data from large, prospective randomized clinical trials will continue to define new standards in adjuvant endocrine therapy.

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