Short review

Start strong or switch? Adjuvant endocrine strategies for postmenopausal women with hormone-sensitive breast cancer

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Abstract

Women are at considerable risk of recurrence in the first few years following initial treatment for early breast cancer. To reduce the risk of recurrence, including distant metastases, those with hormone-sensitive breast cancer receive adjuvant endocrine treatment. Lymph node metastases are a predictor of high risk of early recurrence and distant metastases; however, a significant number of women with node-negative disease will also develop distant metastases. This is of concern, because the development of distant metastases is associated with a high risk of breast cancer death. Studies in postmenopausal women showed that an aromatase inhibitor (AI) as initial, upfront treatment reduces early recurrence, including distant metastases, compared with tamoxifen. The three available AIs (letrozole, anastrozole, and exemestane) are approved for adjuvant use. Upfront letrozole or anastrozole improved time to distant metastasis in patients included in the Breast International Group 1-98 and Arimidex, Tamoxifen, Alone or in Combination trials, respectively. Of note, the beneficial effects of letrozole on distant disease were already observed in the first report at 2 years of follow-up and confirmed in the updated results with 50 months of follow-up. Here, we discuss the available data for all AIs and strategies to be taken into account for patient management, with a special focus on the effects of available options on early recurrences and metastasis risk.
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Keywords: Aromatase inhibitors; Letrozole; Anastrozole; Exemestane; Breast cancer

1. Introduction

Surveillance data show that, like women worldwide, European women are more likely to be diagnosed with breast cancer than any other cancer. In 2006 in Europe, the most common form of cancer was breast cancer (429,900 cases), accounting for 13.5% of all cancer cases; in women, breast cancer is the leading cause of cancer death (16.7%). Decreasing mortality has been noted in younger women, but mortality is still increasing in older women [1].

Following primary surgical treatment, long-term follow-up indicates that nearly one half (45%) of breast cancer patients will experience a recurrence, with the greatest risk among postmenopausal women. Recurrence risk peaks in the first few years after surgery [2]. In one study of postmenopausal women with breast cancer who received adjuvant tamoxifen therapy (N = 4145; 75% with estrogen receptor-positive disease [ER+]), the cumulative risk of distant metastases peaked to 3.2% at 2 years, and the overall cumulative recurrence rate was 4.2% at 2 years after successful surgery [3]. Recurrence events include both loco-regional, contralateral, and distant metastases, with the latter accounting for the majority of relapse events [4]. Compared with local recurrence, the appearance of distant metastases is associated with poorer survival [5].
The selective estrogen receptor antagonist tamoxifen had been the mainstay, upfront adjuvant therapy in women with ER+ disease. Five years of tamoxifen therapy demonstrated a 41% decrease in the annual risk of recurrence and a 34% decrease in the risk of death in women with ER+ disease [6]. However, the approval of three third-generation aromatase inhibitors (AIs), anastrozole, letrozole, and exemestane, has expanded the choice of treatment for physicians and patients in this setting. Multicenter trials such as the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [7] or the Breast International Group 1-98 (BIG 1-98) study [8,9] report a significantly superior disease-free survival (DFS) benefit for anastrozole or letrozole, respectively, when compared with tamoxifen as initial upfront therapy. Switching treatment to an AI after 2–3 years of initial tamoxifen has also been demonstrated to be superior to continuing with tamoxifen for 5 years in terms of DFS [10,11]. It is not yet clear if one treatment strategy is superior to the other, or if one strategy is of particular benefit to specific subpopulations. Here we review the risk of early recurrence following primary surgery and how effective AIs and tamoxifen are at reducing this risk. This may assist physicians in discussing therapeutic options with their patients.

2. Early recurrence risk and the risk of distant metastases

There is a peak of recurrence early on at 2 years post surgery, but there is an ongoing risk of recurrence that persists for up to 15 years [2,6]. The average hazard of recurrence was 4.3% per year for the time between years 5 and 12 [2] (Fig. 1) [12,13]. Women with positive nodes [2] and higher-grade tumors were more likely to recur compared with women with negative nodes or lower-grade tumors. Positive nodal status also confers a greater risk for early recurrence (Fig. 1), as well as an increased risk of distant metastases.

Distant metastases are the most common recurrence event. Using a cancer registration database, recurrence was computed in breast cancer patients diagnosed in 1996 and 1997 in the West Midlands. At a median follow-up of 70 months, 20.6% of women had distant recurrences, and 9.4% of the women had local or nodal recurrences [14]. Similar findings were observed in another retrospective analysis of women with early breast cancer (at a median follow-up of 44 months post surgery), where distant metastases accounted for 58.3% of recurrence events compared with local events (26.1%) or contralateral events (15.6%) [4].

While the presence of positive nodes confers more recurrence risk, even women with negative nodes may experience recurrence with distant metastases. In a study quantifying the risk of delaying primary surgery, 21% of node-negative patients with small (approximately 2 cm) tumors developed distant metastases [15]. When more than one half (51%) of distant metastases occurred within 18 months of follow-up from surgery, 14% of these were in node-negative patients [16].

Addressing the occurrence of distant metastases has importance for patients, because distant metastases are associated with poor survival. One study reported that the 5-year overall survival (OS) probabilities for patients with distant, locoregional, and contralateral recurrences and no relapse events were 41.3%, 59.3%, 83.4%, and 91.7%, respectively [4]. Data from adjuvant chemotherapy and endocrine trials indicate that improvements in distant DFS can signal subsequent improvements in OS [17], suggesting that the risk of metastases may be a better measure of the survival benefit of various therapies.

3. Currently available endocrine therapies for postmenopausal patients: Tamoxifen and aromatase inhibitors

The available adjuvant endocrine therapies for the treatment of postmenopausal women with hormone-sensitive breast cancer include tamoxifen and the third-generation AIs anastrozole, letrozole, and exemestane. Tamoxifen had been the standard adjuvant therapy until recently, but the AIs have shown superiority over tamoxifen in reducing recurrence risk and are currently recommended [18,19].

The Early Breast Cancer Trialists’ Collaborative Group has, since 1984, collected data on more than 300,000 women treated for early breast cancer. Long-term follow-up shows that 5 years of adjuvant tamoxifen in postmenopausal women can almost halve the recurrence rate and reduces mortality by one-third [6,20]. Of concern, however, is the percentage of women who relapse long after tamoxifen therapy is complete. The British breast cancer database study (N = 4159) reported, at a median follow-up of 7.4 years, that relapse rates were 7.4%, 14.5%, and 25.9% at 2.5, 5, and 10 years, respectively, following initial diagnosis [21]. Another concern is the side-effect profile of tamoxifen. Significant adverse events associated with tamoxifen use include venous thromboembolic events, pulmonary embolism, vaginal bleeding, vaginal discharge, ischemic cerebrovascular events, and endometrial cancer [7,22–24]. An excess of serious, life-threatening adverse events.
(i.e., venous thromboembolic events and endometrial cancer) has also been reported to occur with tamoxifen early in the course of adjuvant tamoxifen therapy.

A recent Expert Consensus on primary therapy for early breast cancer addressed the use of the third-generation AIs. Both anastrozole and letrozole were recommended as upfront adjuvant endocrine therapy to be given for 5 years because of the significant reduction in recurrence events associated with their use. Anastrozole or exemestane were recommended as sequential adjuvant therapy in the “switch” setting, where AIs are given following 2–3 years of initial tamoxifen therapy, for a total of 5 years of adjuvant endocrine therapy [25]. There is currently no guidance as to which strategy is optimal. As shown in Fig. 1, after primary surgical therapy, the recurrence rate varies over time, and the timing of when an adjuvant regimen is introduced could be a factor in how effective the treatment is in preventing early relapse. The next section explores the available data on AI use and timing.

4. The efficacy of adjuvant endocrine therapy strategies

4.1. Upfront adjuvant therapy with anastrozole or letrozole

4.1.1. ATAC: Upfront therapy with anastrozole

The ATAC trial (N = 6241) reported the results of a double-blind, randomized comparison of adjuvant anastrozole (n = 3125) with tamoxifen (n = 3116) after 5 years of treatment for early breast cancer in postmenopausal women [7,26]. A third arm combining anastrozole and tamoxifen (n = 3125) was closed after the first results because there was no greater benefit in efficacy. Eighty-four percent of the study population was hormone receptor-positive [26].

At a median of 68 months of follow-up, anastrozole significantly improved DFS by 13% (anastrozole, 575 events vs. tamoxifen, 651 events; hazard ratio [HR] = 0.87; P = 0.01) in the intent-to-treat (ITT) population and DFS in the hormone receptor-positive group (HR = 0.83; P = 0.005) [7]. Improvement of time to distant metastases was also reported in the anastrozole group vs. the tamoxifen group in the ITT population (324 vs. 375 events, respectively; HR 0.86; P = 0.04) but was not significant in the hormone receptor-positive group (HR = 0.84; P = 0.06). OS was not improved with anastrozole in either the ITT or hormone receptor-positive populations (P = 0.7) [7]. An exploratory analysis of the ATAC trial indicates a reduction of 7% in distant metastatic events over 2.5 years, and a greater effect in reduction of contralateral recurrences [27].

At a median follow-up of 100 months, significant improvements in DFS (HR = 0.9; P = 0.025 for the ITT population; HR = 0.85; P = 0.003 for the hormone receptor-positive population), time to recurrence, and contralateral breast cancer continued to be seen with patients receiving anastrozole vs. those on tamoxifen. A significant prolongation in time to distant metastases was met for the first time after 100 months of follow-up in both the ITT (HR = 0.86; P = 0.022) and hormone receptor-positive populations (HR = 0.84; P = 0.022) [28]. However, OS (ITT: HR = 1.00; P = 0.99; HR = 0.97; P = 0.7 for the hormone receptor-positive population) or deaths after recurrence (ITT: HR = 0.91; P = 0.2; HR = 0.90; P = 0.2 for the hormone receptor-positive population) were not statistically different between the two groups, and a numeric benefit in breast cancer mortality in the hormone receptor-positive population was modest (245 anastrozole vs. 269 tamoxifen deaths) [28].

Safety analyses illustrate the difference between the safety profiles of anastrozole and tamoxifen. In a long-term safety analysis (median follow-up of 68 months), women on anastrozole experienced significantly fewer cerebrovascular events (2% vs. 3%; P = 0.03), venous thromboembolic events (3% vs. 5%; P = 0.0004), and endometrial cancer (0.2% vs. 0.8%; P = 0.02) than those receiving tamoxifen. Fractures (wrist, humerus, arm, and spine) were significantly more frequent in the anastrozole group compared with the tamoxifen group (11% vs. 8%, respectively; P < 0.0001), and there were numerically more ischemic cardiac events with anastrozole than with tamoxifen (4% vs. 3%) [29]. The increased yearly fracture episode rate noted during treatment (2.93% vs. 1.90%, a 55% relative increase) did not continue into the post-treatment follow-up period, where the rate for patients taking anastrozole was very similar to that for patients taking tamoxifen (incidence rate ratio 1.03, non-significant) [28].

There appears to be an excess of serious adverse events noted early in tamoxifen therapy that is not seen with anastrozole. The rate of venous thromboembolic events was particularly elevated within the first 2 years of the combined anastrozole/tamoxifen regimen, and in the monotherapy groups, women on anastrozole were 39% less likely to experience a venous thromboembolic events (odds ratio 0.61; P < 0.0001). This risk of venous thromboembolic events with tamoxifen remained elevated throughout the 5-year study period [30]. Endometrial abnormalities also were most commonly noted during the first year of tamoxifen therapy, with a trend toward more events associated with tamoxifen (44% vs. anastrozole 27%; odds ratio 0.52; P = 0.17) [31].

However, an excess of non-breast cancer deaths has been observed in the anastrozole group. An increase in the incidence of deaths due to new primary cancers was reported in the anastrozole arm of ATAC (54 vs. 38), mostly due to lung (15 vs. 8) and colorectal cancer deaths (12 vs. 9) [29]. In the 100-month follow-up of the ATAC trial, more lung (42 vs. 24), colorectal (56 vs. 36), and head and neck (12 vs. 5) new primary cancers (at non-breast cancer sites before recurrence) occurred with anastrozole than with tamoxifen [28].

4.1.2. BIG 1-98: upfront therapy with letrozole

In the BIG 1-98 randomized, phase 3, double-blind trial, postmenopausal women with operable, invasive, hormone receptor-positive breast cancer (N = 8028) were randomized to one of four treatment groups: (A) 5 years of letrozole, (B) 5 years of tamoxifen, (C) 2 years of letrozole followed by 3 years of tamoxifen, or (D) 2 years of tamoxifen followed by 3 years of letrozole [8]. In an analysis at 25.8 months of follow-up, letrozole significantly improved DFS by 19% over tamoxifen...
(Table 1) [8,9,32], including a significant benefit in the time to distant recurrence of 27% (HR = 0.73; 95% CI 0.70–0.93; P = 0.003) [8] (Fig. 2) [8,9,11,26,27,33]. Of note, although time to distant recurrence was not a protocol-specified end point, it was defined in the statistical-analysis plan to allow a comparison with data from the ATAC trial, which had time to distant recurrence as a predefined end point. Letrozole was associated with a 14% reduction in mortality relative to tamoxifen, which did not reach statistical significance. There were fewer overall (166 vs. 192) and cancer-related (111 vs. 154) deaths with letrozole than with tamoxifen. With these data taken together, it is tempting to speculate that a survival advantage may occur with longer follow-up [8]. In a recent subset analysis restricted to the monotherapy arms of the BIG 1-98 trial, at 51 months’ median follow-up, a significant benefit of letrozole on DFS relative to tamoxifen (HR = 0.82; 95% CI 0.71–0.95; P = 0.007) was confirmed (Table 1) [9].

Another analysis examined the predictors of early recurrence (N = 7707) in the BIG 1-98 trial at a median follow-up of 2 years. The analysis focused on early recurrence, defined as the first proven, invasive local, contralateral breast, regional, or distant metastases at any site. Events from the two monotherapy arms (A and B) were included at 2 years along with events from the two sequential arms (C and D) occurring 2 years from the start of therapy. Overall, 3.7% of women relapsed early, with more women on tamoxifen relapsing early vs. the letrozole group (4.4% vs. 3.0%). The most common site of early relapse in either group was distant metastases. Compared with tamoxifen, letrozole reduced the risk of early distant metastases by 30% (tamoxifen, 125 events vs. letrozole, 87 events) after adjusting for prognostic factors, with the difference in hazards becoming evident about 1 year after randomization [32]. The choice of endocrine treatment was among the significant predictive factors for early relapse (HR = 0.69; P = 0.002) (Table 2) [32].

A difference in the safety profile was also evident for letrozole and tamoxifen. The BIG 1-98 exploratory analysis at 51-month follow-up, which confirmed the results of the primary core analysis, found that letrozole was generally well tolerated [8,9]. Tamoxifen was associated with significantly more thromboembolic events, endometrial abnormalities, hot flashes, night sweats, and vaginal bleeding. Letrozole was associated with more fractures, arthralgia, and low-grade hypercholesterolemia, which may be more a consequence of the cholesterol-lowering

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### Table 1

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Primary end point</th>
<th>Patient sample</th>
<th>Follow-up (median)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary core analysis [8]</td>
<td>Disease-free survival</td>
<td>8010, all patients in 2- and 4-arm randomization options</td>
<td>25.8 months</td>
<td>HR = 0.81; 95% CI 0.70–0.93; P = 0.003</td>
</tr>
<tr>
<td>Predictor for early recurrence analysis [32]</td>
<td>Any “early” recurrence</td>
<td>7707 patients in 4-arm option</td>
<td>2 years</td>
<td>HR = 0.69; 95% CI 0.5–0.9; P = 0.002</td>
</tr>
<tr>
<td>Monotherapy analysis [9]</td>
<td>Disease-free survival</td>
<td>4922 of patients in monotherapy arms A and B</td>
<td>51 months</td>
<td>HR = 0.82; 95% CI 0.71–0.95; P = 0.007</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

* Any recurrence or invasive contralateral breast cancer or second non-breast malignancy or death without a prior cancer event.

* Arms A–D; patients in sequence arms (C,D) censored 1 month after switch at 2 years.

* Within 2 years.

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Fig. 2. Recurrence rates in major aromatase inhibitor clinical trials indicate distant metastases are the most common site of recurrence [8,9,11,26,27,33]. ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG 1-98, Breast International Group 1-98; ABCSG 8, Austrian Breast and Colorectal Study Group 8; ARNO, Arimidex–Nolvadex; ITA, Italian Tamoxifen Arimidex; IES, Intergroup Exemestane Study; ANA, anastrozole; LET, letrozole; EXE, exemestane; TAM, tamoxifen.
effects of tamoxifen. The overall incidence of cardiac events did not significantly differ between the arms, although more patients in the letrozole arm experienced cardiovascular events other than ischemia and cardiac failure [9].

4.1.3. Upfront therapy: Anastrozole vs. letrozole
The Femara Anastrozole Clinical Evaluation (FACE) trial has completed recruitment. This trial directly compares the efficacy and safety of upfront adjuvant therapy with anastrozole or letrozole in postmenopausal women with node-positive breast cancer [34]. In the absence of the results from this direct comparison, an indirect comparison of the ATAC and BIG 1-98 trials may provide some insight into their relative efficacy in the upfront adjuvant setting. Fig. 3a and b shows the relative reduction in recurrence rate between the ATAC and BIG 1-98 trials. In this comparison, letrozole is associated with fewer early relapses overall (Fig. 3a) [13,32] and, particularly, fewer early distant metastases at 2 years (Fig. 3b) [27,32], compared with both anastrozole and tamoxifen. In both studies, the AI was superior to tamoxifen in preventing early relapse in the 2–2.5 years post surgery.

4.2. Switch studies with anastrozole or exemestane
In the switch setting, women receive a 5-year course of adjuvant endocrine therapy, beginning with 2–3 years of tamoxifen and then switching to an AI for the remaining 2–3 years of treatment. Note, a “switch analysis” includes all events only from the point of switch (after 2–3 years of adjuvant tamoxifen therapy) to study end and, as such, reports results on a select patient population, because those who relapsed while on adjuvant tamoxifen are excluded from the analysis.

4.2.1. Intergroup Exemestane Study
In the Intergroup Exemestane Study (IES), an international, double-blind trial, postmenopausal women who were free of disease after 2–3 years of adjuvant tamoxifen were randomized to continue tamoxifen (n = 2380) or to switch to exemestane (n = 2320) to complete the 5-year adjuvant endocrine regimen [11]. In an early analysis at a median follow-up of 30.6 months, exemestane significantly improved DFS (HR = 0.68; P < 0.001) and distant DFS (HR = 0.66; P = 0.0004). There were no significant differences in OS between exemestane and tamoxifen (HR = 0.88; P = 0.37) [11]. The effect of exemestane on DFS was confirmed in a later analysis (median follow-up 55.7 months) and was evident in both the ITT population (HR = 0.76; P = 0.001) and the ER+ or unknown disease subset (HR = 0.75; P = 0.001). Overall, this constituted a 3.3% and a 3.4% absolute improvement in DFS at 2.5 and 5 years post randomization, respectively. Exemestane also significantly prolonged the time to distant recurrence in the ITT groups and the ER+/unknown group (HR = 0.83; P = 0.03 for both) [35].

In the ITT analysis of IES, neither exemestane nor tamoxifen patients had a statistically significant survival benefit (222 deaths exemestane vs. 261 deaths tamoxifen; 15% relative reduction in risk of death; P = 0.08). However, in the ER+/unknown group, there were significantly fewer deaths in the exemestane vs. the tamoxifen group (210 deaths vs. 251 deaths, respectively; 17% relative reduction in risk of death; P = 0.05). An analysis adjusting for potential confounders confirmed the survival benefit in the ER+/unknown group (HR = 0.83; P = 0.04) but not in the ITT group (P = 0.07) [35]. The significant reduction in the risk of distant metastases seen in all subjects at 30.6 months of follow-up resulted in a marginal OS improvement in women with ER+/unknown disease with longer follow-up.

The results of the IES safety analysis were similar to previous comparative studies of an AI and tamoxifen. Tamoxifen patients experienced significantly more venous thromboembolic
events and serious gynecologic events than those on exemestane, while exemestane was associated with numerically more cardiovascular events and significantly more fractures and complaints related to the musculoskeletal system [35].

4.2.2. Italian Tamoxifen Arimidex Trial

A small, prospective, randomized, open-label study, the Italian Tamoxifen Arimidex (ITA) trial comprised almost solely ER+, node-positive, postmenopausal women (N = 448) who had completed 2–3 years of tamoxifen for primary breast cancer. The target accrual was not met due to concurrent competing trials in Italy and the great variation in duration of tamoxifen therapy [36]. Following initial tamoxifen therapy, women were randomized to either continue tamoxifen or switch to anastrozole, completing a 5-year treatment plan [36]. Preliminary results at 36-month median follow-up show anastrozole significantly lengthened both DFS (HR = 0.35; P = 0.001) and local recurrence-free survival (HR = 0.15; P = 0.003) relative to tamoxifen. However, the benefit of anastrozole on distant metastases-free survival (HR = 0.49; P = 0.06) and OS (P = 0.1) was not statistically significant [36]. An analysis at 64 months confirmed the earlier results that anastrozole significantly improved recurrence-free survival (HR = 0.56; P = 0.01) and also event-free survival (HR = 0.57; P = 0.005) [37]. There was no significant effect on OS at 36, 52, or 64 months of follow-up [36–38]. Safety analysis revealed that although anastrozole was associated with significantly more adverse events compared with tamoxifen (203 vs. 150; P = 0.04), the tamoxifen arm had significantly more life-threatening events and hospitalizations (33 of 150 vs. 28 of 203 events; P = 0.04) [36].

The ITA safety analysis revealed that significantly more women taking anastrozole had an adverse event (anastrozole, 209 of 223 women vs. tamoxifen, 151 of 225 women; P = 0.000), but the overall incidence of serious (life-threatening, required hospitalization) events was similar between groups (37 anastrozole vs. 40 tamoxifen events; P = 0.7). Serious gynecologic problems were more frequent with tamoxifen than anastrozole (12 vs. 2 events, respectively; P = 0.006), and lipid metabolic disorders were more frequent with anastrozole (8.1% anastrozole and 1.4% tamoxifen; P = 0.01). There were numerically more musculoskeletal disorders and bone fractures with anastrozole; and while the difference was not statistically significant, it is an effect that appears to be associated with AI use [37].

4.2.3. Pooled analysis: GROCTA 4B and ITA

The results of the ITA trial (N = 448) and another switch trial, the Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group (GROCTA 4B) trial (N = 380), were pooled to assess mortality at a median of 78 months. This analysis was prospectively planned when the ITA study was designed. The design of the GROCTA 4B trial was similar to that of the ITA trial, except that aminogluthethimide was substituted for anastrozole [39]. Women who switched from tamoxifen to anastrozole or aminogluthethimide had improved all-cause mortality relative to tamoxifen (HR = 0.61; P = 0.007) and better breast cancer-related mortality (HR = 0.61; P = 0.025). There were 74 deaths (51 breast cancer-related) and 48 (33 breast cancer-related) deaths in women receiving tamoxifen and aminogluthethimide/anastrozole, respectively [39]. Several factors should be considered when evaluating these results. First, both trials failed to meet planned enrollment and separately are not powered to assess mortality in the switch setting. Second, the lack of standardized procedures regarding treatment for recurrence may have introduced bias. Third, aminogluthethimide is an older AI, less potent than the current third-generation AIs, and is no longer used to treat breast cancer. Fourth, the survival advantage observed here for the AIs may also be attributed to the early use of and a carryover effect of tamoxifen, as reported in a recent review of adjuvant tamoxifen studies [6,39].

4.2.4. The Arimidex—Nolvadex 95 study

The Arimidex—Nolvadex (ARNO) 95 study, a prospective, randomized open-label trial, was intended to evaluate DFS in hormone receptor-positive postmenopausal women (N = 979) who switched to anastrozole (n = 489) or continued tamoxifen (n = 490) after an initial 2-year recurrence-free treatment period with tamoxifen [40]. Anastrozole was associated with a 34% improvement in DFS (HR = 0.66; P = 0.049) and 47% in OS (HR = 0.53; P = 0.045). The significant benefit of anastrozole on DFS (HR = 0.61; P = 0.023) and OS (HR = 0.48; P = 0.026) was still present after adjusting for prognostic factors including age, tumor size and grade, lymph node status, and the type of primary surgery. The number of women with distant metastases was similar between the anastrozole (27 events, 5.5%) and tamoxifen groups (33 events, 6.7%) [40].

Women who switched to anastrozole had a lower incidence of serious adverse events than those on tamoxifen (101 of 445 [22.7%] vs. 139 of 452 [30.8%], respectively), with the difference attributed primarily to serious endometrial events in women receiving tamoxifen (odds ratio [OR] = 0.66; P = 0.065). Musculoskeletal events were more common with anastrozole (11.7% vs. 4.8%); however, the bone fracture rate was identical between groups. Tamoxifen patients had numerically more deep venous thromboses (1.3% vs. 0%), while anastrozole patients reported more ischemic cardiovascular events (2% vs. 0.9%), due mostly to complaints of angina in four patients [40].

It should be noted that the time of randomization in the IES and ARNO 95 studies, occurring after women had received 2–3 years of adjuvant tamoxifen and remained disease-free, eliminated women who were either resistant to tamoxifen (thereby selecting for patients with hormone-sensitive disease) or those who had a recurrence in the initial period of tamoxifen therapy. This may have eliminated women with more aggressive disease and those who had a higher risk of early relapse in the first 1 or 2 years following primary surgical therapy [41].

4.2.5. Austrian Breast and Colorectal Study Group 8 trial

The Austrian Breast and Colorectal Study Group 8 (ABCWG 8) trial (N = 3700) randomized newly diagnosed,
postmenopausal women with hormone receptor-positive early breast cancer who had not received any endocrine therapy, to either 5 years of tamoxifen or 2 years of tamoxifen followed by 3 years of anastrozole. ABCSG 8 was a “sequential trial,” because it randomized patients immediately following surgery and included all events from the beginning of the first adjuvant endocrine agent to study end. This differs from “switch” data, because randomizing patients at the point of switch would select for patients who had successfully undergone 2–3 years of tamoxifen therapy and exclude those who had relapsed. The primary end point was event-free survival, including loco-regional, contralateral, or distant metastatic recurrences, while secondary end points included safety and OS.

For the switch analysis (N = 2529), at a median follow-up of 30 months, the HR for DFS was 0.62, corresponding to a 38% reduction in events for patients taking anastrozole over patients taking tamoxifen (P = 0.011) [42]. The 30-month sequential analysis (N = 2926) from this trial included events from study start to study end, and thus all the early relapse events that occurred in the first few years with tamoxifen. At a median follow-up of 30 months, the analysis showed only a trend toward a DFS benefit for the AI (HR = 0.76; P = 0.07) [42]. Thus, ABCSG 8 is currently the only AI trial that has not reached its primary end point. Therefore, when all early relapse events are included, the sequential strategy did not show a superior DFS benefit when compared with 5 years of tamoxifen.

4.2.6. Combined ARNO 95/ABCSG 8 analysis

A prospectively planned, pooled, “switch” analysis from the ARNO 95 and the ABCSG 8 studies assessed the potential benefit of switching to anastrozole after 2 years of tamoxifen vs. completing all planned therapy with only tamoxifen. The ARNO 95 trial (N = 962) randomized women who remained disease-free after 2 years of tamoxifen treatment, and the ABCSG 8 study (N = 2262) randomized women prior to initiating any tamoxifen use [10].

The primary end point, event-free survival (median follow-up of 28 months), was significantly improved by 40% in women who switched to anastrozole compared with those who remained on tamoxifen (67 vs. 110 events; HR = 0.60; P = 0.0009). Distant metastases accounted for almost two thirds (62%; N = 110) of recurrence events arising in 3% of anastrozole and 5% of tamoxifen patients. This represented a 39% reduction in the risk of distant metastases for women who were randomized to anastrozole (HR = 0.61; P = 0.0067). Distant metastases as a first event were also less likely to occur in anastrozole patients (HR = 0.54; P = 0.0016). No differences in OS were seen in the pooled analysis at 3 years’ post switch (97% anastrozole vs. 96% tamoxifen) [10]. However, a later analysis of the ARNO 95 study at a median follow-up of 30.1 months showed that switching to anastrozole significantly improved OS (HR = 0.53; P = 0.045 by the log-rank test; HR = 0.48; P = 0.025 by the Cox proportional hazards model) [40].

In this combined analysis, bone fractures were significantly more frequent in the anastrozole group compared with the tamoxifen group (34 vs. 16 fractures, respectively; P = 0.015). Women who remained on tamoxifen experienced significantly more thrombosis (12 tamoxifen vs. 3 anastrozole; P = 0.034). Anastrozole patients had a trend toward fewer emboli and endometrial cancers [10].

4.2.7. Combined analysis: ABCSG 8/ARNO 95/ITA

The combined results from three trials, ABCSG 8, ARNO 95, and ITA, resulted in a comparison of anastrozole (n = 2009) with tamoxifen (n = 1997) as switch treatment. Irrespective of a patient’s nodal status, HR status, or tumor size, anastrozole significantly reduced the risk of recurrence by 41% (HR = 0.59; P < 0.0001) (Fig. 2). Improvement was also noted in event-free survival (HR = 0.55; P < 0.001), distant recurrence-free survival (HR = 0.61; P = 0.002), and OS (HR = 0.71; P = 0.04) [43].

However, this combined analysis did have some limitations. All three studies were open-label, which could introduce bias when the treatment is known. The patient populations also differed because ITA subjects were mostly node-positive, whereas ARNO 95/ABCSG 8 patients were mostly node-negative. Also, more women in the ITA trial had undergone a mastectomy and received prior chemotherapy. The ABCSG 8 trial included subjects with grade 1 or 2 tumors, while patients with higher-grade tumors were included in the other trials, and there were differences in doses and duration of tamoxifen therapy. In an attempt to minimize the impact of these limitations, individual patient data were used in this analysis. Two of the studies (ITA, ARNO 95) randomized patients at the time point when 2 years of tamoxifen therapy were completed, while the ABCSG 8 trial randomized patients upfront, prior to any tamoxifen treatment (Fig. 1). Yet, this combined analysis only included events after 2 years of tamoxifen in each of these three trials. Thus, the analysis is not directly applicable to a prospective strategy to start with tamoxifen with the intent to switch to an AI after 2 years [43]. ABCSG 8, the largest trial in this combined analysis, was the only trial that did not show an event-free survival benefit with anastrozole and also found a similar incidence of deaths between the arms (44 tamoxifen vs. 42 anastrozole) [44].

5. Considerations when choosing an adjuvant AI treatment strategy

5.1. Efficacy

Recurrence is a continuing worry for women after breast cancer surgery. One study (N = 1550) reported that 212 (13.7%) subjects had an early relapse (≤3 years) with tamoxifen, and even more (421 patients or 31.5%) had a late relapse (≥3 years) event [45]. The risk hazard also changes over time. A cohort of 9279 women from five randomized National Surgical Adjuvant Breast and Bowel Project trials receiving chemotherapy for ER− disease or tamoxifen with/without chemotherapy in ER+ disease revealed that the ER− women had an earlier, larger peak in recurrence risk compared with those with ER+ disease. ER+ patients, however, had a peak of early relapse risk at 2 years post surgery with a sustained
risk over time, and a “cross-over with ER—patients” at approximately 3.5 years that resulted in a cumulative risk exceeding that of the ER—patients at about 48 months [46].

There is a clear peak in the risk of early relapse in the first few years post surgery [2]. Distant metastases account for the majority of these events, a fact confirmed in both the switching and upfront adjuvant AI trials (Figs. 2 and 3) [8,26,35]. So far, the two AIs approved in the upfront setting have shown significant improvement in time to distant recurrence [8,28]. The significance of improved time to distant recurrence was reached at an earlier time point in the BIG 1-98 trials (25.8 months and confirmed at 50 months) compared with the ATAC trial (100 months).

A limitation in comparing the switching trials is that a select patient population is enrolled because the randomization to tamoxifen or an AI occurs after patients are deemed recurrence-free following 2–3 years of tamoxifen therapy. The IES trial recruited women in this manner (Fig. 1), thus, excluding women who experienced an early recurrence [11]. The only truly sequential trial, ABCSG 8, randomized women before they received tamoxifen and included events from the 2 years prior to the switch to continued tamoxifen or an AI. Unlike other switch trials, there was no significant DFS benefit in this study [42]. The difference in randomization between most switch trials and trials comparing an AI with tamoxifen as upfront treatment make across-trial comparisons difficult.

The BIG 1-98 trial randomized all patients immediately following surgery and is evaluating both upfront therapy with tamoxifen or letrozole and sequential therapy with both agents in either order. The results from this trial may provide more insight into the benefits of each treatment strategy [8]. Until an optimal AI treatment strategy is defined by ongoing trials, the goal of therapy should be to offer the agent or strategy that is most effective at preventing recurrence, while also taking into account adverse-event profiles, patient preferences, and cost. Because many recurrences occur in the first few years after surgery, particularly in high-risk patients, it seems reasonable to discuss the potential benefit of an upfront AI to reduce early recurrences, including those at distant sites.

5.2. Safety

While the safety profile of tamoxifen is distinct from that of the AIs, the AIs anastrozole, exemestane, and letrozole have similar safety profiles regardless of AI type (steroidal, nonsteroidal) and treatment strategy (upfront, switch, or sequential). Compared with tamoxifen, AI treatment is associated with an increase in musculoskeletal symptoms and bone fractures and a decreased risk of venous thromboembolic events, cerebrovascular events, and endometrial cancer. These differences may account for early withdrawals from tamoxifen treatment, as shown in the ATAC study. There were more tamoxifen than anastrozole withdrawals at both 2.5 years (tamoxifen 226, anastrozole 195) and 5 years (tamoxifen 349, anastrozole 305) [13].

The increased risk of serious adverse events early in tamoxifen treatment (venous thromboembolic events, endometrial cancer) suggests that use of an AI at the earliest opportunity may be the preferred approach [13]. An ATAC risk—benefit analysis integrating adverse event and recurrence data associated with each drug resulted in a risk—benefit index for both anastrozole and tamoxifen. There were significantly fewer events for patients on anastrozole than for patients on tamoxifen; the difference was greatest 1–2 years after the start of treatment. The choice to use an AI as initial treatment instead of tamoxifen would decrease the risk of some recurrences and adverse events associated with tamoxifen [29]. In addition to a discussion of recurrence risk and patient co-morbidities, quality of life and cost issues should be addressed for individual patients [47], but the most realistic treatment plan may be as simple as initiating treatment with the best option available.

5.3. Modeling analyses

Data on the optimal treatment strategy for the use of AIs in early breast cancer is not expected until around 2008, when the final results from BIG 1-98 are expected to be available. It is anticipated that these results will show whether upfront use of an AI or sequential treatment following 2–3 years of tamoxifen optimizes treatment for women with early breast cancer. In the absence of these data, modeling analyses have been developed to predict the potential relative efficacy of the two treatment approaches. The model included recurrence rates from the first 20 years of follow-up from the following studies: BIG 1-98 (51-month subset analysis restricted to the monotherapy arms), updated results from IES and ITA, results reported separately from the ARNO 95 and ABCSG 8 studies, and the first reported results from the National Surgical Adjuvant Breast and Bowel Project B-33 trial. Only results from hormone receptor-positive women and observed hazard ratios were used for end points, including time to recurrence and time lost to recurrence, assuming there were no deaths from other causes, with more weight given to early recurrence. This model indicates that an upfront AI strategy is better than a switching strategy, as evidenced by the lower recurrence rate (17.7% vs. 18.1%) and less time lost (9.3 vs. 10.0) at year 10 [48].

In a similar study, Markov-decision making models were employed to simulate the 10-year DFS in postmenopausal women with hormone receptor-positive invasive breast cancer. Separate models were used for node-positive and node-negative disease [49]. Treatment regimens considered were (1) an AI or tamoxifen alone for 5 years and (2) sequential therapy beginning with tamoxifen (for 2.5 or 5 years) followed by an AI. A modest, absolute 1–2% improvement in the 10-year recurrence risk was apparent for the 2.5 year cross-over regimen compared with the other regimens [49]. Although the outcome of the analysis seems to differ from the former study, it must be stressed that the latter model did have some limitations, thereby limiting its validity. It assumed that the HRs and patient populations were directly comparable between trials using upfront or switch adjuvant therapy and that all AIs provide similar, ongoing benefits. Additionally, the latter model assumed that the end points were uniformly
defined in the trials used in the analysis; this was not the case, because the definition of DFS differed in the ATAC and BIG 1-98 trials.

6. Conclusions

Although the AIs significantly decrease the risk of recurrence compared with tamoxifen [7,8,35], no single AI or regimen has been deemed superior to others for postmenopausal women with hormone receptor-positive early breast cancer. Current guidelines recommend the AIs as upfront adjuvant therapy or as part of a switch adjuvant therapy regimen. Results from the FACE trial and the sequential arms of BIG 1-98, when available, may provide more insight; but until then, indirect comparisons, if interpreted with caution, may aid physicians in determining which AI to give and which treatment strategy to employ.

It is shown that postmenopausal women with hormone-sensitive breast cancer remain at risk for recurrence some years after primary surgery, with the peak risk occurring in the first few years after surgery. Two AIs, anastrozole and letrozole, more effectively prevent recurrence than tamoxifen as initial adjuvant therapy. Letrozole and anastrozole demonstrated significant prolongation in the time to distant metastases in the hormone receptor-positive population in the initial adjuvant setting. Letrozole resulted in a distinct and significant reduction in time to distant recurrence early within the first 2 years of treatment, which was confirmed in the 50-month analysis. The safety profile of AIs in both initial and switch treatment strategies are similar, showing an association with bone loss and joint symptoms, whereas tamoxifen is associated with increased incidence of venous thromboembolic events, endometrial cancer, and cerebrovascular events early in therapy.

Until definitive data are available, the benefits and risks of each approach should be shared with patients. Initiating treatment with an AI is a reasonable approach to reduce early relapse risk, especially early distant metastases, with the potential of leading to an improvement in breast cancer survival. Even if patients are started on tamoxifen, switching to an AI would provide greater protection against relapse than continuing on tamoxifen.

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