Update on Adjuvant Endocrine Therapy in Breast Cancer

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Abstract: Estrogen and progesterone are known to be the driving force in a significant number of breast cancers. Hormonal therapy has been used for many years to decrease the risk of breast cancer recurrence in patients with localized disease, originally in all patients, but now only in patients with tumors overexpressing estrogen and progesterone receptors. Tamoxifen became the gold standard of hormonal therapy after multiple clinical trials and meta-analyses proved its clinical benefits. Aromatase inhibitors have become increasingly important in the management of breast cancers with hormone receptor overexpression. Despite all the advancements, the optimal duration of adjuvant hormone therapy and the role of luteinizing hormone releasing hormone agonists in premenopausal women have not been fully elucidated. This article reviews the literature on adjuvant hormonal therapy in early stage breast cancer with an emphasis on the extended adjuvant tamoxifen trials ATLAS and aTTom, as well as the recently released TEXT and SOFT trial results looking at aromatase inhibitors in premenopausal women.

Keywords: Breast cancer, early stage, adjuvant endocrine therapy, adjuvant hormonal therapy.

1. INTRODUCTION

Hormones are known to play an important role in the etiology, treatment strategy, and recurrence of breast cancer. Hormonal manipulation as an adjunct to breast cancer treatment was documented as far back as 1896, with oophorectomies performed in two premenopausal women with advanced disease [1, 2]. Information from multiple sources suggests that estrogen plays an important role in breast cancer development and progression. Experimental data in rodents, in vitro studies in humans, and observations of increased breast cancer rates with combination conjugated estrogen/progestin agents for postmenopausal hormone replacement all implicate estrogen as a major factor in breast cancer pathogenesis [3,4]. Multiple hormonal manipulation strategies have been attempted with the goals of treating advanced breast cancer, preventing recurrence of localized breast cancer, and as primary prevention.

Hormonal treatment strategies in premenopausal women have included the use of ovarian ablation (surgical removal or radiation of the ovaries), medical ovarian suppression with luteinizing hormone releasing hormone (LHRH) agonists/antagonists, the selective estrogen receptor modulator tamoxifen alone, tamoxifen plus ovarian ablation/suppression (OAS), and inhibition of the conversion of androgens to estrogens (peripheral aromatization) in conjunction with OAS. Tamoxifen was approved by the United States Food and Drug Administration in 1977 for the treatment of advanced breast cancer and originally stood as the gold standard of hormonal therapy. Tamoxifen is a selective estrogen receptor modulator with both antagonist and agonist functions depending on the site of action. It is an antagonist of the estrogen receptor in breast cancer cells, inhibiting translocation and nuclear binding of the estrogen receptor, and ultimately altering transcriptional and posttranscriptional events [5, 6].

In premenopausal women, the majority of estrogen is produced by the ovary, while in postmenopausal women, estrogen production is driven by peripheral aromatization [7]. Aromatase inhibitors have been shown to be useful in the treatment of postmenopausal patients. Aromatase is an enzyme that converts androgens (androstenedione and testosterone) to estrogens (estrone and estradiol). Aromatase is found predominantly in peripheral tissues (e.g. skin, muscle, fat) and leads to low, but stable levels of estrogen [7]. An aromatase inhibitor (AI) can block this pathway of estrogen production almost entirely. However, in premenopausal women, it can actually cause an increase in estrogen levels. A reflex increase in gonadotropin hormone release leads to increased aromatase production in the ovary and an ability to overcome the aromatase blockade. OAS in conjunction with AIs has been evaluated as a method to overcome this reflexic estrogen increase in premenopausal patients. AIs are classified as steroidal (e.g. exemestane) and nonsteroidal (e.g. anastrozole, letrozole).

While the treatment success for all stages of breast cancer has markedly improved over the last century, and the risk of dying from breast cancer has declined partly due to this, women with early stage disease are
still at risk for recurrence and death from their disease even decades after their original diagnoses [8]. Because of this, lengthening adjuvant treatment times with well-tolerated hormonal agents has been evaluated as a strategy for preventing late recurrences and increasing the lifespan of patients with breast cancer [9-11]. However, the optimal agent and length of treatment for both pre- and postmenopausal women has not been fully elucidated. This article reviews the data behind adjuvant hormonal therapy in patients with breast cancer with a focus on the results from the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) and the United Kingdom (UK) Adjuvant Tamoxifen-To offer more (aTTom) trials looking at tamoxifen treatment length, and the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) studies looking at the benefit of ovarian ablation with Tamoxifen or Exemestane in premenopausal women.

2. SELECTION AND METHODOLOGY

The following clinical studies and topics are explored in this review. Adjuvant clinical trial data has been compiled into meta-analyses by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). These meta-analyses evaluated the effect that treatment type (chemotherapy, OAS, tamoxifen, or a combination), treatment length, hormonal receptor status of the tumors, and other clinical characteristics had on clinical outcomes and side effect profiles [8, 12]. In early clinical trials, women were treated with tamoxifen regardless of their estrogen receptor (ER) or progesterone receptor (PR) status. Data has since shown that ER or PR positivity is important in determining who benefits from hormonal therapy. In the EBCTCG analysis, patients with ER-poor (ER measurement < 10 fmol/mg cytosol protein) tumors had no benefit with 5 years of tamoxifen compared to no tamoxifen [8]. Per guidelines published by the American Society of Clinical Oncology (ASCO) and College of American Pathologists in 2010, ER or PR positivity is now defined as greater than or equal to 1% expression on tumor cells using immunohistochemistry [13]. Because of the now well-established importance of hormone receptor status, clinical trials that included HR negative patients oftentimes eliminate these patients from final analyses.

Treatment length with tamoxifen was addressed in two similar studies, ATLAS and aTTom. Prior to these studies, two relatively small trials published in the 1990s showed no benefit of extending tamoxifen treatment beyond 5 years [14, 15]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 actually showed a detriment in disease free survival for patients who continued tamoxifen for 10 years rather than stopping at 5 years [16]. However, it was felt longer follow-up was needed before definitive conclusions could be drawn regarding trials extending tamoxifen treatment beyond 5 years. The global ATLAS and the UK aTTom trials attempted to answer this question and reported results in 2012 and 2013 respectively [10, 11].

Aromatase inhibitor trials in postmenopausal women have taken three main forms: 1) upfront: AI versus tamoxifen; 2) sequential: 1-3 years of tamoxifen followed by an AI versus tamoxifen to complete 5 years; 3) extended adjuvant: 5 years of tamoxifen followed by 5 years of an AI versus nothing. Most only included women with HR-positive disease. More recently, AIs have been studied in premenopausal women. The TEXT and SOFT trials evaluated the role aromatase inhibitors play in premenopausal women treated with OAS and what role OAS has in premenopausal women treated with tamoxifen.

3. RESULTS

3.1. Tamoxifen

3.1.1. Early Breast Cancer Trialists’ Collaborative Group

The benefits of adjuvant tamoxifen and optimal length of treatment were explored by the EBCTCG [8]. This meta-analysis compared 5 years versus 1-2 years of tamoxifen in HR positive patients. Indirect comparison from the overall meta-analyses that 1-2 years is inferior to 5 years of tamoxifen is highly significant (2p<0.00001 for recurrence, 2p=0.0001 for breast cancer mortality). Clinical trials that directly compared 5 years to 1-2 years of therapy included 18,000 women and also showed superiority of 5 years of tamoxifen, with improved recurrence risk ratio (RR) (0.82, 2p<0.00001) and breast cancer death risk ratio (0.91, 2p=0.01). This data supports 5 years of hormonal therapy with tamoxifen in women with ER or PR positive disease as standard of care.

Subsequent analysis was done on over 21,000 women in 20 trials comparing at least 3-5 years of tamoxifen therapy to no tamoxifen [12]. ER-positive patients that received tamoxifen had half the recurrence rate during years 0-4 and a reduction by a third during years 5-9 with the overall recurrence rate reduction 39% (RR 0.61, 2p<0.00001). It appears therefore that there is a carryover effect of tamoxifen...
since women had ongoing benefit from tamoxifen therapy after it was discontinued at 5 years. Tamoxifen’s benefit in ER-positive disease remained with the addition of chemotherapy (i.e., chemotherapy plus tamoxifen is better than chemotherapy alone). Breast cancer mortality was also reduced in the patients receiving tamoxifen, with the yearly rate down almost a third. This benefit was seen from years 0 to 14. The absolute mortality benefit increased over time, with the difference 3% (9% vs. 12%) at 5 years and 9% (24% vs. 33%) by year 15.

Side-effects of tamoxifen included increased uterine cancer incidence, with 9 deaths in the tamoxifen group from uterine cancer versus 1 in the control group (p=0.07) [12]. Death from pulmonary embolism (PE) was also numerically higher in the tamoxifen group (6 deaths versus none), but this difference was not significant (p=0.25). There was a slight excess of death from stroke, but this was counter-balanced by a slight decrease in cardiac deaths in the tamoxifen group.

3.1.2. Adjuvant Tamoxifen: Longer Against Shorter-ATLAS

Two clinical trials addressed the question of extending adjuvant tamoxifen beyond 5 years. Because tamoxifen has a carryover effect, it was felt longer follow-up may show improvement in outcomes. ATLAS was an open-label, international study conducted in 36 countries from 1996-2005 that randomized 12,894 women free of disease after 5 years of tamoxifen to receive 5 more years of tamoxifen or to stop therapy in a 1:1 fashion [10]. ER status was unknown in 37% of patients, and these patients were excluded from the main analyses (although included in the side-effect analysis). 6846 women with ER-positive disease were ultimately evaluated for revised endpoints of recurrence rates and breast cancer mortality.

Follow-up for people enrolled in the trial was 77% at 15 years after diagnosis. Patients assigned to continue tamoxifen for 10 years had a reduced risk of recurrence (RR 0.84, p=0.002), breast cancer mortality (331 vs. 397 deaths, p=0.01), and overall mortality (639 vs. 722 deaths, p=0.01). Absolute breast cancer mortality reduction was 2.8% (12.2% vs. 15%) from years 5-14. The main effects on recurrence and breast cancer mortality were realized in the second decade after diagnosis. The difference in risk ratios for years 5-9 compared to after year 10 in breast cancer mortality was significant (RR 0.97 vs. 0.71, difference in RR: p=0.04). This result may explain why previous trials with shorter follow-up failed to show a benefit for 10 years of tamoxifen versus 5 years.

Increased incidence of certain adverse events were seen with continuing tamoxifen, with the RR for PE (1.87, p=0.01) and endometrial cancer (ECA) (1.74, p=0.0002) increased. There was no mortality difference from PE (0.2% in both groups), and there was a non-significant 0.2% difference (0.4% vs. 0.2%) in mortality from ECA. There did seem to be some protective effect from continuing tamoxifen, as that group had a reduction in the incidence of ischemic heart disease (RR 0.76, p=0.02), with a trend towards improved mortality (p=0.1).

3.1.3. Adjuvant Tamoxifen-To Offer More?-aTTom

Results from aTTom were presented at the 2013 American Society of Clinical Oncology (ASCO) national meeting [11]. This was a UK multi-center trial conducted from 1991-2005, randomizing women after 5 years of tamoxifen to either receive tamoxifen to complete 10 years of therapy or to stop tamoxifen. Over 60% of patients were ER-unknown, with 80% of these patients assumed to be ER-positive if their status had been known based on the established frequency of ER or PR positive breast cancers.

6,953 women were recruited to the study. Patients that continued tamoxifen had significantly reduced breast cancer recurrence (p=0.003) and breast cancer mortality (392 vs 443 deaths, p=0.05). Overall mortality was reduced (849 vs. 910 deaths) but was not significant (p=0.1). As in the ATLAS trial, reductions in breast cancer recurrence and mortality, as well as overall mortality, were more pronounced in the later years (more than 9 years). When results from ATLAS were combined with aTTom, OS was improved (p=0.005). There was an increased risk of ECA (RR 2.20, p<0.0001) and death from ECA (37 vs. 20 deaths, absolute hazard 0.5%, p=0.02).

3.1.4. 10 Years Versus 5 Years of Tamoxifen

ATLAS and aTTom provide the strongest evidence to date that patients benefit from continuing on tamoxifen for 10 years. Breast cancer recurrence and breast cancer mortality were improved in both studies. Overall mortality was improved in the ATLAS trial, but this improvement was not significant in the aTTom trial. One explanation for this may be the ER-unknown population included in the aTTom trial, since 60% of patients had unknown ER status. ER-negative patients in this group may have confounded the OS results. Prior to continuing tamoxifen for 10 years, the clinician should discuss the risks of increased PE and ECA diagnoses, and the potential for increased risk of death from ECA with the patient.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Key eligibility criteria</th>
<th>N= patients</th>
<th>Sites</th>
<th>Primary endpoint</th>
<th>Primary endpoint results</th>
<th>OS difference</th>
<th>Other</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC [17,18]</td>
<td>Upfront A vs. upfront T vs. A+T Placebo controlled</td>
<td>HR+/ No neo-adj chemo</td>
<td>9366</td>
<td>21 countries</td>
<td>DFS</td>
<td>A&gt;T HR: 0.83 (p=0.013) A&gt;A+T HR: 0.81 (p=0.006) A+T=T HR: 1.02 (p=0.8)</td>
<td>No A&gt;T HR: 0.95 (p=0.4)</td>
<td>No A&gt;T DFS A&gt;T: 89.4%, 87.4%, 87.2% A&gt;T DFS in HR+ HR: 0.86 (p=0.003) A&gt;T ARR: 4.3% at 10 yrs</td>
<td>3 yr DFS A&gt;T: 89.4%, 87.4%, 87.2% A&gt;T ARR: 4.3% at 10 yrs</td>
</tr>
<tr>
<td>ARNO 95 [19]</td>
<td>Sequential: T x 2 yrs, then A or T to finish 5 yrs</td>
<td>HR+ pT1-3, pN0-2 No chemo</td>
<td>979</td>
<td>Germany</td>
<td>DFS</td>
<td>A&gt;T HR: 0.66 (p=0.049)</td>
<td>Yes A&gt;T HR: 0.53 (p=0.045)</td>
<td>3 yr DFS absolute diff 4.2%</td>
<td>Fewer AEs in A (22.7%) vs. T (30.8%)</td>
</tr>
<tr>
<td>ABCSG 8 [20]</td>
<td>Sequential: T x 2 yrs, then A or T to finish 5 yrs</td>
<td>HR+, G1-2 No chemo Low-int risk</td>
<td>3714</td>
<td>Austria</td>
<td>RFS</td>
<td>A=T HR: 0.80 (p=0.06) Compensating for cross-over: A+T HR: 0.76 (95% CI 0.60-0.97)</td>
<td>No A&gt;T HR: 0.87 (p=0.34)</td>
<td>DRFS 22% risk reduction (HR 0.78; 0.60-0.99)</td>
<td>More bone pain in A vs. T (3.6% diff, p&lt;0.02) More uterine d/o in T vs. A (20.2% vs. 14.1%, p&lt;0.001)</td>
</tr>
<tr>
<td>ITA [21,22]</td>
<td>Sequential: T x 2-3 yrs, then A or T to finish 5 yrs</td>
<td>ER+, ax LN+</td>
<td>448</td>
<td>Italy</td>
<td>DFS</td>
<td>A&gt;T HR: 0.35 (p=0.001)</td>
<td>Yes A&gt;T HR: 0.35 (p=0.001)</td>
<td>A&gt;T HR: 0.35 (p=0.001)</td>
<td>More AEs in A vs. T (203 vs. 150, p=0.04) More SAE in T (22% v 13.9%, p=0.04) More gyn changes (11.3% v 1%, p=0.0002) Sig more gyn problems in T (8 ECA vs. 1)</td>
</tr>
<tr>
<td>ABCSG 8 + ARNO 95 [23]</td>
<td>Planned, event-driven combined analysis</td>
<td>HR+ No chemo</td>
<td>3224</td>
<td>Germany, Austria</td>
<td>EFS</td>
<td>A&gt;T HR: 0.60 (p=0.0009)</td>
<td>No 3 year OS A vs. T: 97% v 96% p=0.16</td>
<td>3 yr DFS A&gt;T: 95.8% vs. 92.7%</td>
<td>Sig A&gt;T fractures, nausea, trend toward bone pain</td>
</tr>
<tr>
<td>ABCSG 8 + ARNO 95 + ITA [24]</td>
<td>Meta-analysis</td>
<td></td>
<td>4006</td>
<td>Germany, Austria, Italy</td>
<td>DFS</td>
<td>A&gt;T HR: 0.59 (p&lt;0.0001)</td>
<td>Yes A&gt;T HR: 0.71 (p=0.0377)</td>
<td>A&gt;T DFS HR: 0.55 (p=0.0001) A&gt;T DFS HR: 0.61 (p=0.0015)</td>
<td>Sig T&gt;A thromboses, trend toward emboli and ECA</td>
</tr>
<tr>
<td>BIG 1-98 [27]</td>
<td>Upfront T vs. upfront L Double-blind</td>
<td>HR+</td>
<td>8010</td>
<td>Internatio nal</td>
<td>DFS</td>
<td>L&gt;T HR: 0.81 (p=0.003)</td>
<td>No L=T HR: 0.87 (p=0.08)</td>
<td>5 yr DFS estimates 84% v 81.4%</td>
<td>Sig T&gt;L: VTE, gyn bleeding, ECA (0.3% v 0.1%), hot flashes Sig L&gt;T: fractures (5.7% v4%), grade 3-5 cardiac events, arthralgia, HLD</td>
</tr>
<tr>
<td>BIG 1-98 [32]</td>
<td>Sequential T/L or L/T vs. L alone</td>
<td>HR+</td>
<td>6182</td>
<td>Internatio nal</td>
<td>DFS</td>
<td>T/L=L HR: 1.05 (0.84-1.32) L/T=L HR: 0.96 (0.76-1.21)</td>
<td>No T/L=L HR: 1.13 (0.83-1.53) L/T=L HR: 0.90 (0.65-1.24)</td>
<td>T/L vs. L/T vs. L 5 yr DFS: 86.2% vs. 87.6% vs. 87.9% T/L vs. L/T vs. L 5 yr OS: 92.4% vs. 93.7% vs. 93.4%</td>
<td>Sig T&gt;L: VTE, gyn bleeding, hot flashes, night sweats Sig L&gt;T: HLD, arthralgia, myaliga, fractures</td>
</tr>
<tr>
<td>IES [33]</td>
<td>Sequential: T x 2-3 yrs, then E vs. T to finish 5 yrs Double-blind</td>
<td>ER+ or unknown</td>
<td>4742</td>
<td>37 countries</td>
<td>DFS</td>
<td>E&gt;T HR: 0.68 (p=0.001)</td>
<td>No E=T HR: 0.85 (p=0.08) exluded HR: 0.83 (p=0.05)</td>
<td>3 yr DFS 91.5% vs 86.8%</td>
<td>Sig E&gt;T: arthralgia, diarrhea, osteoporosis, visual disturbances Sig T&gt;E: gyn axs, vag bleed, muscle cramps, VTE, 2nd primary non-breast CA</td>
</tr>
</tbody>
</table>
Results in the following section are grouped by greater than 5 years of hormonal therapy, respectively.

### 3.2. Aromatase Inhibitors

Tables 1 and 2 summarize trial results for studies examining 5 or less years of hormonal therapy, or greater than 5 years of hormonal therapy, respectively. Results in the following section are grouped by specific AI.

**Table 2: Clinical Trials of Hormonal Therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Key eligibility criteria</th>
<th>N= patients</th>
<th>Sites</th>
<th>Primary endpoint</th>
<th>Primary endpoint results</th>
<th>OS difference</th>
<th>Other</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAM [36]</td>
<td>E alone x 5 yrs vs. after T x 2-3 yrs for 5 yrs (amended after IES results)</td>
<td>HR=</td>
<td>9766</td>
<td>9 countries (Europe, Japan, US)</td>
<td>DFS</td>
<td>E=T/E HR: 0.97 (p=0.6)</td>
<td>No 5 year OS 91% in both (HR 1.00)</td>
<td>No difference in distant mets T/E vs E DFS 5 yrs: 85% v 86% T/E vs E RFS 5 yrs: 11% v 10% (p=0.29)</td>
<td>T/E&gt;E: gyn sx, VTE, endometrial abn E&gt;T/E: MSK AEs, osteoporosis, fractures, HTN, HLD, CHF</td>
</tr>
<tr>
<td>aTTom [11]</td>
<td>Extended: T x 5 yrs, then T to complete 10 yrs vs. stopping ER+ or unknown</td>
<td>6953</td>
<td>UK</td>
<td>BCA recurrence</td>
<td>T&gt;none recurrence: 580 vs. 672 (p=0.003)</td>
<td>No Overall mortality: 849 vs. 910 deaths (p=0.1)</td>
<td>Reduction in BCA recurrence, BCA mortality, and overall mortality increased with time</td>
<td>T&gt;E: ECA deaths (absolute hazard 0.5%, p=0.02)</td>
<td>T+ or T+AG 5 yrs, then A or nothing x 3 yrs HR+ stage I or II pT1-3a, N+/-</td>
</tr>
<tr>
<td>ABCSG 6a [25]</td>
<td>Extended: T or T+AG 5 years, then A or nothing x 3 yrs</td>
<td>1135</td>
<td>Austria</td>
<td>RFS</td>
<td>T+A&gt;T HR: 0.62 (p=0.031)</td>
<td>No T+A=T HR: 0.89 (0.59-1.34, p=0.57)</td>
<td>Distinct mets only significant difference (16 vs. 35 events, p=0.034) 10 yr recurrence T+A vs. T: 7.1% v 11.8%</td>
<td>T+ or T+AG 5 yrs, then A or nothing x 3 yrs HR+ stage I or II pT1-3a, N+/-</td>
<td>Austrian multi-center</td>
</tr>
<tr>
<td>MA-17 [9, 28-30]</td>
<td>Extended: T x 4.5-6 yrs, then L vs. plac x 5 more yrs Double-blind, placebo-controlled</td>
<td>5187</td>
<td>Canada, UK</td>
<td>DFS</td>
<td>L&gt;plac HR: 0.57 (p=0.00008)</td>
<td>Yes, in ER+/PR+ patients L&gt;plac HR: 0.58 (0.37-0.90) Yes, in Ax LN+ patients L&gt;plac HR: 0.61 (p=0.04)</td>
<td>4 yr DFS L vs. plac: 93% v 87% (p&lt;0.001) No OS diff in ITT analysis OS diff when factoring for cross-over</td>
<td>Sig L&gt;p: hot flashes, arthritis, arthralgia, myalgia Sig p&gt;L: vaginal bleeding Trend toward more osteoporosis with L (p=0.07)</td>
<td>HR+</td>
</tr>
<tr>
<td>NSABP B-33 [35]</td>
<td>Extended: T x 5 yrs, then E vs. plac x 5 more yrs Double-blind, stopped early</td>
<td>1598</td>
<td></td>
<td>DFS</td>
<td>E&gt;plac HR: 0.68 (p=0.07)</td>
<td>No Not enough deaths to draw conclusions</td>
<td>E vs. plac 4 yr DFS: 91% vs. 89% E vs. plac 4 yr RFS: 96% vs. 94%, 56% RRR (p=0.004)</td>
<td>Grade 3 toxicity higher in E vs. plac (9% v 6%)</td>
<td>HR+</td>
</tr>
</tbody>
</table>

**Abbreviations:** A=anastrozole; T=tamoxifen; A+T=anastrozole and tamoxifen concurrently; E= exemestane; L= letrozole; T/L= tamoxifen followed by letrozole; LT=letrozole followed by tamoxifen; T/E=tamoxifen followed by exemestane; plac=placebo; AG=aromatinogluthimide; vs=versus; yrs=years; adj=adjuvant; chemo=chemotherapy; HR+/+=hormone receptor; G1-2=grade 1-2; int=intermediate; ax=auxiliary; LN=lymph node; HR=hazard ratio; ARR=absolute reduction of recurrence; DRFS=distant relapse free survival; EFS=event free survival; diff=difference; ERR=event rate ratio; AE=adverse events; SAE=serious adverse events; CVA=cerebrovascular accident; VTE=venous thromboembolism; d/o=disorders; ECA=endometrial cancer; MSK=musculoskeletal; gyn=gynecologic; sig=significant; CHF=congestive heart failure; sx=symptoms; HLD= hyperlipidemia; CA=cancer; BCA=breast cancer; abn=abnormalities.
post-menopausal women [17]. This was a three-arm, double-blind placebo controlled study with patients randomized after primary surgery and chemotherapy (if indicated) to adjuvant upfront tamoxifen (TAM) alone plus placebo, anastrozole (ANA) alone plus placebo, or concurrent tamoxifen and anastrozole (TAM+ANA). HR-negative and unknown patients were included in this study, but a planned subgroup analysis by HR status was included in the protocol. About 20% of patients in each treatment group received chemotherapy. The primary endpoint of disease-free survival (DFS) was significantly longer in the ANA group than in either the TAM or TAM+ANA groups. The absolute 3-year DFS benefit of ANA was 2% compared to TAM (89.4% vs. 87.4%) and 2.2% compared to TAM+ANA (89.4% vs. 87.2%), indicating that the combination is not more effective than TAM alone. 10-year updated results showed continued DFS improvement in the ANA group compared to TAM, with a 10-year DFS benefit in HR-positive patients of 4.3% [18]. However, there was no overall survival difference between the TAM or ANA alone groups, even when evaluating only HR-positive patients.

Three main studies evaluated the sequential use of anastrozole after 2-3 years of tamoxifen: Arimidex-Nolvadex (ARNO) 95, The Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG-8), and the Italian Tamoxifen Anastrozole (ITA) trials. In the ARNO 95 trial, DFS and OS were significantly improved in the anastrozole group, with an absolute 3 year DFS benefit of 4.2% (93.5% vs. 89.3%) and OS difference of 2.6% (96.9% vs. 94.3%) [19]. The ABCSG-8 trial included over 3000 women with early-stage breast cancer; 75% of patients had T1 tumors and 75% were node-negative [20]. Patients in the sequential group receiving tamoxifen followed by anastrozole had a 20% decrease in risk of recurrence, but this only trended towards statistical significance (HR 0.80; p=0.06). When compensating for patients that crossed over to the anastrozole group following the release of other study results, this difference was significant (HR 0.76; 95% CI 0.60-0.97). OS was the same between the two groups. The ITA included over 400 ER-positive, lymph node-positive women [21]. DFS was significantly improved in the anastrozole switch group (HR 0.35; 95% CI 0.18-0.68). Updated survival results showed no difference between the two groups, but the study was not powered for this endpoint [22].

An event driven combined analysis of the ABCSG 8 and ARNO 95 trials, as well as a meta-analysis of the ABCSG 8, ARNO 95, and ITA trials, were also published [23, 24]. The meta-analysis showed an OS improvement in the group that switched to anastrozole (HR 0.71; 95% CI 0.52-0.98). Other results from these analyses are included in Table 1.

Another trial looked at extended adjuvant therapy with anastrozole. The ABCSG 6a trial was an extension of a trial that randomized women to tamoxifen alone for 5 years or tamoxifen plus aminoglutethimide (a non-selective, first generation aromatase inhibitor) concurrently for 2 years followed by tamoxifen alone to complete 5 years [25, 26]. Women who were disease free after the 5 years were then randomized to receive anastrozole for 3 years, for a total of 8 years of adjuvant therapy, or to no further therapy. With over 1,100 women in the trial, the primary endpoint of relapse free survival (RFS) was prolonged in the patients that received the additional 3 years of anastrozole (HR 0.62; 95% CI 0.40-0.96), with a recurrence rate at 10 years after surgery of 7.1% in the anastrozole group versus 11.8% in the group assigned to no further treatment. Overall survival was no different between the treatment groups.

In the anastrozole trials, upfront, sequential, and extended adjuvant methods all showed either a relapse free or disease free survival benefit. Overall survival benefit was seen in sequential therapy in the ARNO 95 trial and ABCSG 8/ARNO 95/ITA meta-analysis, with a total duration of adjuvant hormonal therapy of 5 years in these trials. The concurrent use of tamoxifen with anastrozole in the ATAC trial negated the benefits seen when anastrozole was given alone or sequentially. This may be due to the weak agonistic effect tamoxifen has on estrogen receptors which interferes with the effects of anastrozole [17]. Because of this, tamoxifen and anastrozole should not be used in combination. Toxicities in these clinical trials are summarized in Tables 1 and 2. The serious adverse events for patients that received anastrozole were rare, while the most common adverse events were typically musculoskeletal related. When compared to tamoxifen, patients receiving anastrozole typically had less gynecologic problems.

### 3.2.2. Letrozole

Two large randomized phase III trials studied the role of letrozole in adjuvant treatment for post-menopausal women with breast cancer. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.17 trial examined extended adjuvant letrozole after tamoxifen whereas the Breast...
International Group (BIG) 1-98 trial looked at letrozole upfront compared to tamoxifen upfront, as well as sequential therapy with letrozole followed by tamoxifen and vice versa [9, 27]. Tables 2 and 1 respectively summarize results and toxicities from these studies.

MA.17 was a double-blind, placebo-controlled trial that randomized over 5,000 HR-positive women after 4.5-6 years of tamoxifen to letrozole or placebo for 5 more years. The primary endpoint of disease free survival was significantly better for the letrozole group, with 4-year DFS 93% in the letrozole group and 87% in the placebo group. There was no OS difference between the groups in the first analysis. However, exploratory multivariable analysis was undertaken with subsequent publications, and this showed a significant OS benefit with letrozole for patients with axillary lymph node-positive disease, patients that had tumors that were both ER and PR-positive, and for all patients when adjusting for women assigned to placebo that crossed over to letrozole after unblinding [28, 30]. After results emerged from MA.17, patients that had been randomized to receive placebo after tamoxifen were then offered letrozole [31]. Median time after completing tamoxifen was 2.8 years, and patients that accepted letrozole (1579 of 2383 eligible patients) also had significantly improved disease free and overall survival when compared to patients that continued in the placebo group (804 of 2383 patients), showing that exposure to letrozole, even after a prolonged time had elapsed from tamoxifen use, was still beneficial.

BIG 1-98 was a 4-arm, double-blind trial of over 8,000 HR-positive women who were assigned to 5 years of tamoxifen monotherapy, 5 years of letrozole monotherapy, 2 years of tamoxifen followed by 3 years of letrozole, or 2 years of letrozole followed by 3 years of tamoxifen [27]. Comparisons of letrozole alone to tamoxifen alone favored letrozole, with 5 year DFS estimates 84.0% versus 81.4% (DFS HR 0.81; 0.70-0.93). There was no OS difference between the two treatments. Subsequent analysis of the sequential treatment groups compared to letrozole alone was published [32]. There was no difference in DFS or OS between either of the sequentially treated groups and the letrozole alone group, providing evidence that both upfront and sequential treatment with AI are acceptable strategies. Updated OS data of letrozole versus tamoxifen alone showed a trend toward benefit with letrozole, with absolute 5 year OS differences 91.8% versus 90.9% (HR 0.87; 0.75-1.02, p=0.08) [32]. As expected, patients in the letrozole group had more fractures and less thromboembolic events, vaginal bleeding and endometrial cancers (0.1% vs. 0.3%, p=0.18). However, there were also more grade 3-5 cardiac events in the letrozole group (2.1% vs. 1.1%, p<0.001) [27].

3.2.3. Exemestane

A summary of important clinical trials involving exemestane is shown in Tables 1 and 2. The Intergroup Exemestane Study (IES) randomized over 4,000 women after 2 to 3 years of tamoxifen to either continue tamoxifen or switch to exemestane to complete 5 years of therapy [33]. The primary endpoint of disease free survival was significantly better in the group that switched to exemestane, with DFS rates 3 years after randomization of 91.5% versus 86.8%. Updated overall survival results showed a benefit with exemestane when 122 ER-negative patients were excluded from analysis (17% relative risk reduction of death, p=0.05) [34].

Two other major trials involving exemestane were affected by the MA.17 and IES clinical trial results reported prior to the completion of these studies. The NSABP B-33 randomized early stage, HR-positive women after 5 years of tamoxifen to either exemestane or placebo for 5 more years [35]. The MA.17 trial results showing the benefits of extended adjuvant letrozole necessitated the early termination of patient accrual and unblinding of treatment groups in this study, and 44% of patients in the placebo group crossed-over to receive exemestane. In the intention-to-treat analysis, 4 year DFS trended toward improvement with exemestane (91% vs. 89%, p=0.07) and relapse free survival was significantly improved in the exemestane group (96% vs. 94%, p=0.004), even in an under-powered study (due to early termination) with significant cross-over of the placebo group to active treatment with exemestane.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) study was originally designed to evaluate upfront exemestane versus upfront tamoxifen [36]. Trial protocol was later amended upon the release of the IES results that showed sequential therapy with exemestane was better than tamoxifen alone. The amended study enrolled HR-positive women in an open-label randomized trial comparing upfront exemestane for 5 years to tamoxifen for 2-3 years followed by exemestane to complete 5 years of treatment. No differences in DFS or OS were seen between the two groups.
Adverse events in the exemestane trials were similar to those seen in all AI trials and are summarized in Tables 1 and 2. Musculoskeletal events were more common with exemestane, and gynecologic problems were more common with tamoxifen.

### 3.2.4. Aromatase Inhibitor Comparisons

Because anastrozole, letrozole, and exemestane all showed benefit over tamoxifen as adjuvant therapy in post-menopausal women, and absolute disease free survival benefits were similar amongst all AIs, they have generally been considered to have similar efficacies. Clinical trials directly comparing AIs have evaluated this. The NCIC CTG MA.27 compared exemestane to anastrozole as upfront adjuvant therapy in an open-label phase III study [37]. At a median follow-up of 4.1 years, the primary endpoint of event free survival at 4 years was no different between patients taking exemestane versus anastrozole. Another trial comparing letrozole to anastrozole (Femara versus Anastrozole Clinical Evaluation (FACE)), is underway but no results have been released to date [37].

### 3.3. Ovarian Ablation and Suppression

In the EBCTCG analysis of clinical trials involving patients that received ovarian ablation and suppression (OAS) versus those that did not, 15-year recurrence and breast cancer mortality rates were improved (47.3% vs. 51.6%, 2p=0.00001 and 40.3% vs. 43.5%, 2p=0.004 respectively) [8]. The impact was greatest in trials comparing OAS to no adjuvant chemotherapy.

A Cochrane database review on LHRH agonists attempted to determine its optimal use in premenopausal women [39]. Adjuvant LHRH agonist alone compared to older adjuvant chemotherapy regimens alone (i.e. CMF) were similar in recurrence-free and overall survival in ER-positive patients. There was a trend toward improved recurrence-free and overall survival in patients that received LHRH agonists plus chemotherapy versus chemotherapy alone. Conclusions from this review were that LHRH agonists can be beneficial in the adjuvant setting, but direct comparisons using newer generation chemotherapy regimens were needed before more definitive recommendations could be given regarding its use in premenopausal women.

The TEXT and SOFT clinical trials addressed the role of OAS in conjunction with tamoxifen or aromatase inhibitors [40, 41]. The TEXT trial randomized premenopausal patients to receive exemestane or tamoxifen for 5 years with OAS. The SOFT trial randomized 3066 premenopausal women to receive exemestane with OAS, tamoxifen with OAS, or tamoxifen alone for 5 years of therapy. On either trial, women could choose triptorelin (an injectable GnRH agonist), oophorectomy, or ovarian radiation as the method of OAS. A combined analysis of the OAS groups in the TEXT and SOFT trials was reported in June 2014 and included 4690 premenopausal women with early stage breast cancer [40]. After 68 months median follow up, DFS at 5 years was excellent for both treatment groups, 91.1% in Exemestane + OAS (E+OAS) and 87.3% in the Tamoxifen + OAS (T+OAS) group (HR=0.72; p=0.0002), with 28% reduction in the events in the E+OAS group. The rate of freedom from breast cancer at 5 years was 92.8% in E+OAS and 88.8% in T+OAS with a hazard ratio for recurrence of 0.66, (P<0.001). However, with only 194 deaths (4.1% of the patients) on this study, this analysis did not show any overall survival advantage with E+OAS compared to T+OAS. The small absolute benefit of 4 % between the E+OAS and T+OAS in the proportion of patients without breast cancer recurrence at 5 years reflects reductions in local, regional, distant and contralateral events. However the majority (60%) of the first recurrence events, second invasive cancers or death involved recurrences at a distant site.

In the SOFT trial, after a median follow-up of 67 months, analysis of the Tamoxifen alone arm versus the OAS arms revealed the estimated disease free survival rate at 5 years was not different in the T+OAS and Tamoxifen alone arm; 86.6% versus 84.7% respectively (HR for disease recurrence, second invasive cancer, or death, 0.83, P=0.10) [41]. Further analysis did show a significant DFS improvement when adjusting for prognostic factors. The 5-year freedom from breast cancer rate was 85.7% in the E+OAS group compared to 78.0% in the tamoxifen alone group (HR 0.65, 95% CI, 0.49-0.87) in patients that had received adjuvant chemotherapy, a 35% reduction in the events in favor of the E+OAS arm. A total of 350 women younger than 35 years of age participated in the SOFT trial, among these women, the rate of freedom from breast cancer at 5 years was 67.7% for patients assigned to tamoxifen alone, 78.9% for those assigned to T + OAS, and 83.4% for those assigned E+OAS.

The SOFT and TEXT trials provide evidence that OAS with either tamoxifen or exemestane can provide
clinical benefit in select premenopausal, early stage patients with a higher risk of recurrence. However, no overall survival differences have been proven at this time in either the TEXT or SOFT trials. Longer follow-up is required for both trials and the overall survival analysis results are premature at this time, for example, at the time of the initial SOFT analysis, 95% of study participants were alive.

4. CONCLUSIONS

Hormones are known to play an important role in many aspects of breast cancer. Hormonal therapies have been attempted for the treatment of breast cancer for over 100 years, and advances in the strategies used for hormonal manipulation have grown considerably in the past several decades. Several conclusions from the existing literature can be drawn in regards to adjuvant hormonal therapy for the treatment of breast cancer. Patients with HR-sensitive early stage breast cancer should be offered adjuvant hormonal therapy given its proven benefit and good tolerance. The benefit of tamoxifen in HR-positive patients is more pronounced in patients who receive 5 years of therapy compared to 1-2 years. Premenopausal patients should be treated with adjuvant tamoxifen therapy for at least 5 years, and based on new data from the ATLAS and aTTom studies, can be offered treatment for 10 years of adjuvant therapy.

The role of adjuvant ovarian ablation in the management of early stage breast cancer has been unclear. Most studies used this approach as a comparator to no therapy or to first generation chemotherapy, and in both cases OAS was beneficial. The recently released TEXT and SOFT trial results provide evidence that 5 years of exemestane with OAS is more beneficial than tamoxifen with OAS in premenopausal women with early stage breast cancer, but mature survival data are needed. The SOFT trial supports the use of OAS with either tamoxifen or exemestane in a select group of patients with predetermined higher risk of recurrence such as women younger than 35 year of age or women who are deemed candidates for adjuvant chemotherapy and remain premenopausal. OAS plus exemestane also provides another treatment choice for premenopausal women who have contraindications to tamoxifen therapy.

Postmenopausal women with HR-sensitive breast cancer should be offered adjuvant hormonal therapy with an aromatase inhibitor as the preferred treatment choice. This can be as upfront therapy for 5 years, sequentially with 2-3 years of tamoxifen, or as extended adjuvant therapy after 5 years of tamoxifen. If sequential therapy is chosen, both tamoxifen followed by an AI or an AI followed by tamoxifen are acceptable choices based on the results of the BIG 1-98 trial. Tamoxifen alone should be used in patients that cannot tolerate any AI or do not have access to treatment with AIs. There is no evidence that concurrent use of tamoxifen with an aromatase inhibitor is beneficial based on the results of the ATAC study. Currently, no conclusive data exists to recommend a specific aromatase inhibitor over another. Future clinical trials should help determine if there is any clinical benefit to using aromatase inhibitors beyond 5 years.

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