Clinical Medicine Reviews in Oncology

REVIEW

Hormone Receptor Positive Early Breast Cancer: What Role for Aromatase Inhibitors?

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Abstract: Breast cancer is a significant problem worldwide. Five years of Tamoxifen has been the established endocrine adjuvant therapy for both pre- and post-menopausal women for several decades, until the more recent introduction of AI's for use in post-menopausal ER-positive EBC. There are three third generation AI's currently available commercially these include non steroidal (anastrozole and letrozole) and steroidal inhibitors (exemestane). Anastrozole, letrozole and exemestane have all been compared against tamoxifen in randomised phase III studies as upfront monotherapy and all show a significant improvement in disease free survival (DFS). However there has been no overall survival (OS) benefit seen with AI's in any of the upfront trials.

The question of upfront AI versus switch is complicated and is highly debated. Evidence from randomised phase III trials shows an improvement in DFS for all three AI's in the switch setting. The only trial to show a significant survival benefit is the IES trial where patients were switched to exemestane.

More data is required to directly compare the AI's in the upfront setting and study the most appropriate duration of the AI's. There does still appear to be a role for tamoxifen in low risk patients and for intermediate risk patients when used in combination with aromatase inhibitors in the switch setting.

Keywords: Early Breast Cancer (EBC), Aromatase Inhibitors (AI's) Oestrogen receptor positive (ER-Positive)

Clinical Medicine Reviews in Oncology 2010:2 89–98

This article is available from http://www.la-press.com.

Introduction

Breast cancer is a significant problem worldwide. In the UK it is the most common cancer and the third most common cause of cancer death after lung and bowel cancer, with approximately 38000 new cases per year and 12,000 deaths. Each year 1.3 million women are diagnosed with breast cancer and 465,000 will die worldwide.[1,2] Breast cancer prevalence is higher in developed countries although incidence rates are increasing in non industrialised countries.[3]

The incidence of breast cancer increases with age and 75% of women are post-menopausal at time of diagnosis. Oestrogen receptor (ER)-negative tumours tend to occur in young women, the incidence flattens off after 50 years whilst the rate of ER-positive tumours is similar in the under 50's but increases in older women.[4]

The diagnosis and treatment of breast cancer have improved significantly over the last 30 years and subsequently survival rates have also improved. The estimated five-year survival rate for women diagnosed in England and Wales in 2001–2003 was 80%, compared with only 52% for women diagnosed in 1971–1975.[1]

Recurrence risk can be estimated from disease characteristics such as tumour grade and size, hormone receptor status, human epidermal growth factor receptor status (Her2) and the degree of lymph node involvement. It is known that node positive women are at a significantly higher risk of recurrence.[5]

Patients remain at risk of recurrence 10–15 years post diagnosis. For patients with hormone receptor positive disease the risk of relapse is highest during the first 2–3 years following surgery. The risk of late recurrence is also highest for those with hormone receptor positive tumours.[6]The most common type of both early and late recurrences are distant. Statistics show that women with hormone receptor positive breast cancers have a yearly recurrence rate of 1.5–2% between years 5–15 following diagnosis.[6,7] Distant metastases are known to have a negative effect on mortality.[8]

The best characterised molecular predictive markers in breast cancer are the ER, the progesterone receptor (PR) and Her2. The responsiveness of breast tumours to hormone manipulation provides a unique therapeutic opportunity for targeted therapy. The benefit is limited to ER-positive tumours.[4]

Five years of Tamoxifen, an anti-oestrogen has been the established endocrine adjuvant therapy for both pre- and post-menopausal women for several decades, until the more recent introduction of aromatase inhibitors.

Tamoxifen is a selective ER modulator which prevents oestrogen from binding to the ER; it has been shown to significantly reduce the risk of recurrence. The initial hormone adjuvant trials in the 1990's showed a 47% improvement in disease free survival (DFS) and a 26% overall survival (OS) when compared to placebo.[9] The benefits of tamoxifen are independent of age, prior chemotherapy or tumour characteristics including PR status. Tamoxifen has partial oestrogen agonist action which can lead to an increase in the rates of endometrial carcinomas, in addition there is an increase in the number of thromboembolic events in patients on tamoxifen.[10] There has been recent negative coverage of tamoxifen following publication of an article suggesting that although tamoxifen reduces the overall risk of recurrence there is an increase in the incidence of second oestrogen receptor negative tumours which are more aggressive.[11]

This review of the literature looks at the evidence for aromatase inhibitors in early breast cancer (EBC).

Aromatase Inhibitors

Aromatase inhibitors (AI's) represent a significant advance in endocrine therapy for breast cancer. In pre-menopausal women oestrogen is synthesized in the ovaries and enters the breast via the peripheral circulation. In post-menopausal women oestrogen is no longer produced by the ovaries and is mainly synthesized in the adrenals, muscle and adipose tissue through conversion of androgens to oestrogens by the cytochrome P450 enzyme aromatase.[12,13]

The enzyme aromatase converts androstenedione to estrone (E1) and testosterone to oestradiol (E2). Aromatase inhibitors reduce the biosynthesis of oestrogen and therefore act systemically to lower overall circulating levels of oestrogen in post-menopausal women.

Aminoglutethimide was the first clinically available AI. It demonstrated efficacy in the second line treatment of advanced cancer however it lacked selectivity for the aromatase enzyme and was associated with excess toxicity which limited its use.[12]

The second generation AI 4-hyrdoxyandrostenedione (foremestane) is a steroidal inhibitor that resulted in partial or complete responses in unselected post-menopausal women. It was given in injection form and was relatively well tolerated.[14]

There are three third generation AI's currently available commercially these include non steroidal (Anastrozole and Letrozole) and steroidal inhibitors (Exemestane). These third generation compounds are highly selective and inhibit in vivo aromatization by approximately 98% if administered daily.[15]

Effects of AI's in pre-menopausal women are more complex and AI's are ineffective in the presence of pre-menopausal oestrogen levels.[16]

The third-generation AIs have been shown to be superior to tamoxifen in terms of time to progression in patients with known hormone receptor status and have become established as first-line hormonal therapies for advanced breast cancer.[17]

There have been many trials looking at third generation AI's in the adjuvant setting for early breast cancer patients. There are a variety of settings in early breast cancer in which AI's can be used: upfront adjuvant monotherapy, as part of a switch/sequencing strategy and extended adjuvant therapy.

Upfront adjuvant aromatase inhibitors

The three largest trials directly comparing tamoxifen with AI's as monotherapy are ATAC, BIG 198/IBCSG 18-98 and TEAM. BIG 198 and TEAM also included a sequencing arm.

ATAC Trial-Arimidex, Tamoxifen Alone or in Combination

Anastrozole (arimidex) is a potent non steroidal AI, it binds competitively and reversibly to the aromatase enzyme. The biggest trial of adjuvant anastrozole was the ATAC trial in which patients were randomised to anastrozole alone or in combination with tamoxifen versus tamoxifen alone. It was a large multi-centred randomised controlled trial, the primary end point was DFS and secondary endpoints included time to recurrence (TTR), incidence of new contralateral breast cancer (CBC) and time to distant recurrence (TTDR).

The initial analysis at 33 months showed a superior DFS in the anastrozole alone arm compared with the tamoxifen alone arm hazard ratio (HR) 0.78 (95% CI 0.65–0.93; p = 0.0005). There was no benefit seen in the combination arm when compared to tamoxifen alone.[18]

A second analysis performed after a median 47 month follow up again showed superior DFS when compared to tamoxifen alone, 86.9% at 4 years for anastrozole compared with 84.5% in the tamoxifen arm HR 0.82 (95% CI 0.7–0.96: p = 0.014). The absolute difference in DFS increased over time, 1.5% in the intention to treat group which included some ER-negative patients (8% ER-negative, 8% unknown) and 1.7% in the hormone receptor positive group. No benefit was seen in the combination arm and this arm was discontinued after the 2nd analysis.[19]

At 68 months follow up the majority of patients had completed 5 years of treatment. Anastrozole continued to show superior DFS when compared to tamoxifen, HR 0.83 (95% CI 0.73–0.94; P = 0.0058) in the hormone receptor positive group.[13,18] There was no statistically significant advantage seen in OS.

In January 2008 a further analysis was performed at a median follow up of 100 months, the results confirmed a DFS benefit of anastrozole over tamoxifen HR 0.85 (95% CI 0.76–0.94; p = 0.003). At 5 years there was an absolute difference in recurrence of 2.8% and with 4.8% at 9 years. There was no OS benefit although there was a non significant trend towards improved breast cancer specific survival in the latest analysis. A significant reduction in the incidence of CBC for all randomised patients was seen.[20]

Anastrozole was associated with lower rates of endometrial cancer (0.2% vs. 0.8%; p = 0.02) and thromboembolic events (2.1% vs. 3.5%) than tamoxifen. There was also a reduction in ischaemic cerebrovascular events, vaginal bleeding and hot flushes. An increased incidence of fractures, joint symptoms and carpel tunnel were observed.[18,20–22] Withdrawals due to adverse events were significantly less common with anastrozole (11.1%) than tamoxifen. (14.3%).

BIG 198

The other large trial looking at both upfront monotherapy and sequencing was the BIG-198 trial. Women were randomly assigned to receive 5 years of tamoxifen monotherapy, 5 years of letrozole monotherapy, or 2 years of treatment with one agent followed by 3 years of treatment with the other.[23]

The trial was initially reported in 2005 at a median follow-up of 25.8 months at which point it showed

letrozole significantly reduced the cumulative incidence of breast-cancer relapse as compared with tamoxifen. DFS was significantly greater in the letrozole group than in the tamoxifen group (HR, 0.81; 95% CI 0.70–0.93; p = 0.003).[23] This difference became evident one year after randomization, and there was an absolute difference of 3.4% at five years.

Of note a significant reduction in the risk of distant recurrence with letrozole, as compared with tamoxifen HR 0.73 (95% CI 0.60–0.88; p = 0.001) was seen.

The study was unblinded after the initial analysis and women in the tamoxifen monotherapy group were allowed to cross over to letrozole, 25.2% of patients selectively crossed over to letrozole.[23]

A second analysis was published in 2009 after a median follow up of 71 months, DFS was not significantly improved with either sequential treatment as compared with letrozole alone, tamoxifen followed by letrozole HR 1.05 (99% CI 0.84–1.32), letrozole followed by tamoxifen, HR 0.96 (99% CI, 0.76–1.21).[24]

The updated analysis of monotherapy in the BIG 198 trial confirmed that, as compared with tamoxifen alone, letrozole monotherapy significantly reduces the risk of recurrence of disease, especially at distant sites .There is no significant difference in OS between women assigned to treatment with letrozole and those assigned to treatment with tamoxifen (HR for letrozole, 0.87; 95% CI, 0.75–1.02; P = 0.08).[24]

TEAM Trial—Tamoxifen Exemestane Adjuvant Multinational Trial

The TEAM trial compared upfront tamoxifen to exemestane monotherapy and has recently reported the first analysis after 2.75 years of follow up. Compared with tamoxifen monotherapy, exemestane was associated with a non significant improvement in DFS HR 0.89 (95% CI, 0.77–1.03; p = 0.12) and a significant difference in relapse free survival (RFS) HR 0.85 (95% CI, 0.72–1.00; p = 0.056), and time to first distant metastasis HR 0.81 (95% CI, 0.67–0.98; P = 0.028). No between-group differences were observed for time to CBC or OS, and no unexpected safety issues were reported. Patients ≥70 years old and those with N1 tumours had significant better DFS on exemestane compared to those on tamoxifen.[25,26] High rates of early discontinuation of tamoxifen and early switch to exemestane may have affected the results and longer follow up is needed.

In 2004, based on results of the IES trial, TEAM was modified to include a sequencing arm from tamoxifen to exemestane at 2.5–3 years, these results are reported later in the review.

The results of these trials in combination with a recent meta-analysis of monotherapy with an AI versus tamoxifen showed at 5 yrs, AI therapy is associated with an absolute 2.7% decrease in breast cancer recurrence (10.7% vs. 13.4%, relative decrease 20%, p = 0.00004). There appeared to be greater proportional decreases in isolated local recurrence (30%, p = 0.003) and in contralateral disease (38%, p = 0.003) than in distant recurrence (12%, p = 0.04).[27]

Evidence suggests that AIs are not equivalent in terms of potency of oestrogen suppression and that there may be differences in clinical efficacy in EBC. The question over which is the most effective aromatase inhibitor for patients with early breast cancer remains. There are three recent trials which hope to answer this question; FACE, MA.27 and GIM-3-FATA.[28–31]

FACE-Femara Anastrozole Clinical Evaluation

The FACE trial compare upfront monotherapy with letrozole 2.5 mg or anastrozole 1 mg daily for up to 5 years in post-menopausal, hormone receptor-positive, node-positive breast cancer patients. These patients are thought to be at the highest risk of recurrence. The primary objective was DFS, whilst the secondary objectives were safety, OS, time to distant metastases, time to CBC and breast cancer specific survival.[28] This phase III randomized controlled multicentre study recruited 4000 patients and completed enrolment in February 2008. The results are currently awaited.[29]

MA.27 Trial

The ongoing MA.27 trial is currently comparing adjuvant monotherapy with either anastrozole 1 mg daily or exemestane 25 mg and, initially planned to analyse the role of concurrent celecoxib. Post-menopausal patients with receptor-positive breast cancer are being stratified according to nodal status and prior adjuvant chemotherapy, and randomized to receive exemestane (25 mg/day) or anastrozole (1 mg/day) for 5 years. In addition, each of these two groups were at first randomly assigned to receive either celecoxib

(400 mg twice daily) or placebo (twice daily), for 3 years. Celecoxib is a COX-2 inhibitor which is thought to interrupt the AKT pathway which serves as a signalling intermediate for receptors such as Her2.

The primary end point of the trial is DFS, and secondary end points include OS, time to distant recurrence, evidence of CBC, and long-term clinical and laboratory safety. The MA.27 trial plans to enroll 6830 patients, and began in 2004, the researchers expect to take 6 years to complete accrual. Due to reports of cardiotoxicity, randomization to the celecoxib arms was closed in 2005.[30]

GIM-3-FATA Trial

This NCI Phase III Study is comparing Anastrozole, Letrozole and Exemestane, Upfront (for 5 Years) or sequentially (for 3 Years After 2 Years of Tamoxifen), as Adjuvant Treatment of Post-menopausal Patients with Endocrine-Responsive Breast Cancer, it is currently recruiting.[31] The primary end point is DFS and the main secondary endpoints include OS, distant metastasis free survival, breast cancer free survival and cumulative incidence of CBC.

The results of these trials will hopefully help answer which is the most appropriate aromatase inhibitor for upfront adjuvant monotherapy.

Sequential treatment/switch trials

The concept of switching was initially designed to reduce the development of tamoxifen resistance.[32] Sequential therapy with tamoxifen and aromatase inhibitors has been investigated as an adjuvant treatment regimen in several trials.

Patients in the sequencing trials were randomized shortly after diagnosis, whereas those in the switching trials were randomized at the switch point. Therefore only those who did not relapse within the first 2–3 years were randomized in the switch trials.

A key consideration is which AI to use after switching. Exemestane and anastrozole both have indications after 2–3 years of tamoxifen, whereas letrozole is not indicated for switching. Although no direct comparisons of exemestane and anastrozole have been conducted in switching trials, the preponderance of current evidence is in favour of exemestane, which is approved in more than 20 European countries and was the first AI approved for switching.

Sequential Anastrozole

A meta-analysis of three separate trials, ARNO 95, ABCSG-8 and the ITA showed that switching to an anastrozole after 2–3 years of tamoxifen is superior to continuing with tamoxifen alone.[33] Switching resulted in a significant improvement in DFS HR 0.59 95% CI 0.48–0.74 $P < 0.001$. The benefit of anastrozole over tamoxifen was irrespective of nodal status, receptor status previous chemotherapy or tumour size. Event free survival including the occurrence of CBC and distant metastases were also reduced.[34,35] The meta-analysis suggested a 29% improvement in OS however, it should be noted that the results are inconsistent across the three studies, the patient populations were quite different.

ARNO—Arimidex-Nolvadex/ABCSG-8

The results of these two phase 3 trials conducted by the Austrian Breast Cancer Study Group (ABCSG-8) in collaboration with the German Adjuvant Breast Cancer Group (ARNO 95) were combined. They compared 5 years of tamoxifen vs. sequential tamoxifen for 2 years followed by 3 years of anastrozole. In both trials approximately 75% of patients were node negative. The primary end point was recurrence-free survival (RFS); secondary end points included distant RFS and tolerability.

Patients in the ARNO 95 trial were randomised after completing the initial tamoxifen period whereas in the ABCSG-8 trial patients were randomised at diagnosis. Switching to anastrozole after 2 years lead to a significant improvement in event free survival (EFS) compared with those who continued with tamoxifen alone.

The HR for a loco regional recurrence, a distant recurrence, or a CBC at 3 years was 0.60 (95% CI 0.44–0.81) in the crossover group compared with the group treated with 5 years of tamoxifen. Again, there was a significantly lower risk for distant relapse in the anastrozole group (HR 0.61, 95% CI 0.42–0.87). The latest update of the ABCSG-8 trial suggested an OS improvement although this was not statistically significant. HR 0.77 $P = 0.25$.[36]

ITA—Italian Tamoxifen Anastrozole trial

This trial investigated the efficacy of switching to anastrozole for women already receiving tamoxifen.

After 2–3 years of tamoxifen treatment, postmenopausal, node-positive, ER-positive patients were randomized to receive either anastrozole or to continue tamoxifen, giving a total duration of 5-years treatment. The primary end point was DFS and secondary endpoints were EFS, OS and safety.

At a median follow-up time of 64 months 63 events had been reported in the tamoxifen group compared with 39 in the anastrozole group HR 0.57 (95% CI 0.38–0.85 *P* = 0.005). RFS was significantly higher in the anastrozole group HR 0.56 (95% CI 0.35–0.89 P = 0.01). OS was also longer in the anastrozole group 0.56 (95% CI 0.28–1.15 *P* = 0.1) but this was not statistically significant. The updated analysis confirmed that switching to anastrozole after the first 2–3 years of treatment improved EFS and RFS of postmenopausal, node-positive, ER-positive EBC patients already receiving adjuvant tamoxifen.[35]

IES-Intergroup Exemestane Study

Following 2 to 3 years of tamoxifen therapy, patients were randomly assigned to receive exemestane, or to continue on tamoxifen for the remainder of 5 years' total treatment. Compared with standard tamoxifen for 5 years, switching to exemestane midcourse significantly improved DFS at a median follow-up of 30.6 months, which was characterized by a 32% reduction in risk of recurrence, new CBC, or death, which corresponded to an absolute DFS benefit of 4.7% at 3 years after random assignment.

After a median follow-up of 55.7 months, 809 events contributing to the analysis of DFS had been reported (354 exemestane, 455 tamoxifen); unadjusted HR 0.76 (95% CI 0.66–0.88; p = 0·0001) in favour of exemestane, absolute benefit 3.3% (95% CI 1.6–4.9) by end of treatment (i.e. 2.5 years after randomisation) The updated analysis of IES lends support to the rationale for switching adjuvant therapy to exemestane after 2–3 years of tamoxifen in postmenopausal patients who remain free of recurrence after treatment for EBC.[37]

An update presented at the congress of the European Cancer Organisation (ECCO) in September 2009 showed a significant reduction (18%) in the risk of DFS events HR = 0.82 (95% CI 0.73–0.92; P = 0.0009), compared to women who continued on tamoxifen for a full five years of treatment. In addition, IES showed that exemestane prolonged OS with a 14% reduction in the risk of dying HR = 0.86 (95% CI 0.75–0.99; P = 0.04). These results demonstrate that the benefits of treatment are maintained in long term follow-up.[38] Exemestane is the first and only AI to have demonstrated improved OS in a randomised, double-blind trial. The OS benefit is maintained at 91 months follow up. The switching strategy appears to minimise the adverse risks of both agents.

BIG 1-98 (sequential arm)

The BIG 1-98 trial had a sequential trial, arm in which patients were randomised shortly after diagnosis. In the early sequential adjuvant therapy arms of this 4-arm trial patients received either 2 years of letrozole therapy followed by 3 years of tamoxifen therapy or 2 years of tamoxifen therapy followed by 3 years of letrozole therapy. The primary end point was DFS. The Kaplan–Meier estimates of the percentage of patients who remained disease-free at 5 years after randomization were 87.9% in the group that was assigned to letrozole alone, 87.6% in the group that was assigned to letrozole followed by tamoxifen, and 86.2% in the group that was assigned to tamoxifen followed by letrozole. The estimated DFS was 84.6% for the tamoxifen monotherapy arm this was on the basis of the intention-to-treat analysis in which 39.5% of women in the tamoxifen-monotherapy group crossed over to letrozole.[23]

In the analyses of sequential treatments, neither tamoxifen followed by letrozole nor letrozole followed by tamoxifen showed superiority over letrozole alone. The analysis showed that treatment with letrozole for 2 years followed by tamoxifen yielded outcomes similar to those seen with letrozole monotherapy (87.9% vs. 87.6%) regardless of nodal stage.[23] Based on the results of BIG 1-98 it appears that a sequential strategy remains an appropriate option for intermediate or low risk patients.

TEAM (sequential arm)

In 2004, based on results of the IES trial, the TEAM trial was modified to include a sequential arm, patients were randomised to tamoxifen for 2.5–3 years followed by exemestane for 2.5–3 years or exemestane for 5 years. This was the first trial powered to test superiority of 5 years of AI therapy versus a sequential strategy. The primary end point was DFS and secondary endpoints were OS, RFS and safety. The results at

five years show DFS in the sequential arm 85.7% vs. 85.4% P = 0.604 in the exemestane arm. There was no difference in OS or time to recurrence between the two arms. In subgroup analysis there was no difference in DFS rates for either node-negative or node-positive women.[39]

Extended Adjuvant Therapy

Current practice is to give five years of adjuvant hormones. Several studies have looked at extending this period. The aTTom trial randomised women between continuing for a further 5 years of tamoxifen and completing treatment at five years. No significant reduction in recurrence has yet been seen in aTTom, the results are however consistent with preliminary findings from the ATLAS trial, which reported a DFS but not OS advantage to longer tamoxifen.[40,41]

Combining results from these two large studies indicate that continuation of tamoxifen beyond the first 5 years reduces recurrence over the next few years, but further follow-up is needed to assess reliably the longer-term effects on recurrence and the net effects, if any, on mortality.[40] Letrozole is the only aromatase inhibitor that is currently approved for use in the extended adjuvant setting. Extended anastrozole was studied in the Austrian breast and colorectal cancer study group trial 6a (ABCSG-6a). The numbers were small but the results support the use of extended adjuvant aromatase inhibitors.[42]

MA.17 Trial

The MA.17 trial looked at extended adjuvant letrozole. Women were randomised after 5 years of tamoxifen to 5 years of letrozole or placebo. Letrozole was started within 3 months of completing tamoxifen. At a median follow-up of 30 months, letrozole significantly improved DFS the primary end point, compared with placebo HR for recurrence or CBC 0.58 (95% CI 0.45–0.76; $p < 0.001$). Furthermore, letrozole significantly improved distant DFS HR 0.60 (95% CI 0.43–0.84; P = 0.002) and, in women with node-positive tumors, overall survival HR 0.61 (95% CI 0.38–0.98; P = 0.04). On the basis of the first interim analysis the MA.17 trial was unblinded and all patients in placebo group were offered letrozole, 2/3rds accepted. Clinical benefits, including an OS advantage, were also seen in women who crossed over from placebo to letrozole after unblinding, indicating that tumours remain sensitive to hormone therapy despite a prolonged period since discontinuation of tamoxifen.[43,44] For MA.17, a 2005 report showed an OS advantage in the node-positive subgroup; this was not seen in the most recent results, probably because of a high crossover rate. Extended adjuvant letrozole is now recommended by the ASCO, NCCN and St Gallen guidelines to protect women against the ongoing risk of relapse in the post tamoxifen years. It is not known if this strategy of prolonged treatment improves survival when compared with earlier switching.

NSABP B-33 Study

This was a randomized, placebo-controlled, double-blind clinical trial to evaluate exemestane (25 mg/day) as extended adjuvant therapy (NSABP B-33). The trial included clinical stage $T_{1–3}$ $N_{0–1}$ M_0 endocrine-sensitive post-menopausal breast cancer patients who completed at least 5 years of tamoxifen therapy and were disease-free at the time of tamoxifen discontinuation. The primary aim of the trial was to determine whether adjuvant exemestane, for 2 years, after 5 years of tamoxifen therapy would prolong DFS compared with placebo. Secondary endpoints were OS and RFS.

When accrual to the B-33 trial was initiated, no other information existed on benefit from aromatase inhibitors in this setting. However, when the interim analysis results from MA.17 were published demonstrating a benefit from letrozole in patients who had completed 5 years of tamoxifen B-33 was stopped, the treatment assignment unblinded, and exemestane offered to women in the placebo group. The outcome analysis with 30 months of median follow-up based on the original random assignment (ITT), showed a 32%, borderline statistically significant reduction in 4-year DFS (91% vs. 89%; relative risk [RR] 0.68; p = 0.07)) and in a statistically significant 56% decrease in 4-year RFS (96% vs. 94%; RR = 0.44; p = 0.004).[45]

Discussion

Based on available evidence the consensus from the 11th St Gallen International expert meeting in September 2009 was that aromatase inhibitors should be part of standard endocrine therapy for post-menopausal women although tamoxifen may still be a good option for some low risk, node negative patients.[46]

In the UK the National Institute for Clinical Excellence (NICE) states that anastrozole, exemestane and letrozole, within their licensed indications, are recommended options for the adjuvant treatment of early ER-positive invasive breast cancer in post-menopausal women.[47] Currently letrozole and anastrozole are both licensed for the adjuvant treatment of post-menopausal women with hormone receptor-positive invasive EBC (primary therapy), and the treatment of EBC in post-menopausal women who have received prior adjuvant tamoxifen therapy (sequential therapy). Exemestane is licensed for the treatment of EBC only after prior adjuvant tamoxifen therapy.

Anastrozole, letrozole and exemestane have all been compared against tamoxifen in randomised phase III studies as upfront monotherapy and all show a significant improvement in DFS. The absolute reduction in recurrence with the use of aromatase inhibitors is approximately 3%. However there has been no OS benefit seen with aromatase inhibitors in any of the upfront trials. There was a non significant trend towards improved breast cancer specific survival in the latest analyses of ATAC and BIG 198. The TEAM trial monotherapy arm reported at 2.75 years follow up showed a significant difference in RFS and time to distant metastases with exemestane but only a trend towards improved DFS. It has not yet shown an OS benefit.

Both letrozole and anastrozole are licensed for upfront therapy however there is currently no available data comparing the two agents head to head.

The latest updates of the ATAC and BIG 1-98 trials show a significant DFS benefit for anastrozole and letrozole over tamoxifen as monotherapy. BIG 1-98 also showed that letrozole monotherapy significantly reduces the risk of recurrence of disease, especially at distant sites.

In subgroup analyses of the ATAC trial, the benefit of anastrozole was seen predominantly in patients who had not received adjuvant chemotherapy and those with node-negative disease, whereas in the BIG 1-98 trial, the greatest benefit of letrozole was in patients who had received chemotherapy and in those with node-positive disease or large tumours.[20]

In the BIG 1-98 trial, ER-positive tumours had a similar reduction in the risk of a DFS event associated with letrozole irrespective of their PR status, whereas the ATAC trial showed a beneficial effect of anastrozole mainly in patients with ER-positive and PR -negative tumours.

Letrozole significantly reduces the rate of distant recurrences when compared to tamoxifen and it is known that distant recurrence has a negative impact on mortality. In the advanced setting letrozole has demonstrated the greatest clinical benefit as first line hormone treatment and in vivo leads to more potent oestrogen suppression. The most significant effect of letrozole was seen in patients with larger tumours or positive nodes, suggesting the benefit is greatest in high risk patients.

The GIM-FATA and the FACE trials are expected to help answer the question of the most appropriate aromatase inhibitor for upfront adjuvant monotherapy.

The question of upfront AI versus switch is complicated and is highly debated. Anastrozole, exemestane and letrozole have all been tested in the switch setting. Evidence from randomised phase III trials shows an improvement in DFS for all three aromatase inhibitors. This is also seen in a meta-analysis of the anastrozole trials.[33] The IES trial shows a significant OS benefit for those switched to exemestane.[37,38]

A more recent meta-analysis of all the AI trial data including the exemestane trial data, divided patients into two cohorts: those patients who never received tamoxifen (upfront) and those who received tamoxifen before taking an AI (switch). The first cohort did not show an OS benefit but the second cohort did.[27]

Subset analyses in the meta-analysis with respect to PR status, age, tumour grade and nodal status revealed no apparent heterogeneity between the proportional reductions in recurrence and no indication of an increase or decrease in non-breast deaths with AIs.[27]

The meta-analysis is in contrast to the TEAM trial sequencing arm which has recently reported at 5 years follow up and showed no significant difference in DFS, OS or time to recurrence in the sequencing arm when compared to tamoxifen monotherapy.[39]

One important issue that needs to be addressed in the switch studies is the potential bias introduced at the randomization point. Patients in sequencing trials were randomized shortly after diagnosis, whereas those in switching trials were randomized at the switch point. Therefore only those who did not relapse within the first 2–3 years were randomized. The removal of this poorly responsive group could account for the ability of AIs to achieve a mortality

benefit in the more hormonally responsive patients who made it through the first 2 or 3 years to the randomization point.[48]

Less women are now receiving tamoxifen as monotherapy despite the lack of overall survival benefit for upfront AI's. Post-menopausal women who are currently being commenced on tamoxifen tend to be the low risk patients, this will subsequently effect the use of the switch setting as well as the role of extended adjuvant letrozole. The MA.17 trial demonstrated that extended treatment with letrozole beyond 5 years of tamoxifen decreased the rate of relapse and the greatest benefit was seen in high risk women.

With more women receiving AI's upfront the next question to be addressed is the appropriate duration of treatment with AI's. The SOLE trial is studying the role of letrozole extension, it is a phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 Years of prior adjuvant endocrine therapy for post-menopausal women with hormone-receptor positive, node positive early stage breast cancer.[49]

The other relevant issues when considering choice of oestrogen suppression are tolerability, safety and cost.

All three AIs have similar toxicity profiles. Compared with tamoxifen they are associated with a significantly reduced incidence of endometrial cancer, venous thromboembolism, hot flushes, and vaginal discharge. Conversely, AI's are associated with an increased risk of osteoporosis, bone fractures, and musculoskeletal pain. The clinical relevance of the small increased risk of cardiovascular events and hypercholesterolaemia with AIs compared to tamoxifen warrants further investigation. Switching limits the patient's exposure to either class of drug. As these two classes of drugs have different safety profiles this additional limited exposure to either agent is likely to mitigate the risk of serious complications.[50]

Aromatase inhibitors have significant cost implications across primary and secondary care. Anastrozole has an annual cost of £891.80 and is the least expensive AI drug available costing 17% less than letrozole and exemestane. As per the product license, one year's treatment costs £1,084 for letrozole and £1,080 for exemestane. The cost of one year's treatment with tamoxifen is £34.[51] The first patent for anastrozole is due to expire in June 2010, once the patent expires it is likely that several companies will begin manufacturing generic anastrozole. Anastrozole will subsequently become significantly cheaper.

In summary the evidence for aromatase inhibitors suggest that they do have a significant role in management of EBC in post-menopausal ER-positive tumours. Aromatase inhibitors significantly improve DFS in both the upfront, switch and extended adjuvant setting however the only survival benefit seen so far has been in the switch setting. Exemestane is the only AI associated with a statistically significant survival benefit in the switch setting. Letrozole improves DFS in extended adjuvant treatment however the use in this setting is likely to reduce with the increase in use of the aromatase inhibitors upfront.

More data is required to directly compare the aromatase inhibitors in the upfront setting and study the most appropriate duration of the aromatase inhibitors. There does appear to still be a role for tamoxifen in low and intermediate risk patients and when used in combination with aromatase inhibitors in the switch setting.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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