

Aromatase Inhibitors for Treatment of Breast Cancer

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Abstract: Breast cancer remains the commonest malignancy amongst women and its incidence continues to increase worldwide. This inexorable rise in numbers of women suffering from the disease is particularly notable in those countries which previously had a relatively low incidence of breast cancer but have now adopted Western lifestyles with changes in reproductive behaviour and greater usage of the oral contraceptive pill. These epidemiological observations emphasize the hormone dependency of breast cancer and the importance of endocrine factors for tumour initiation and promotion. There has been a resurgence of interest in hormonal therapies with the advent of third generation aromatase inhibitors (AI) which represent the most significant advance in endocrine management of breast cancer since the introduction of tamoxifen 3 decades ago.

This article will recount the historical development of endocrine therapies and the biological rationale for hormonal manipulation as a therapeutic goal. The application of AI's in the clinical setting will be critically discussed with citation of seminal studies. Like many novel agents for treatment of breast cancer, AI's were initially used in the advanced disease setting where they offered advantages over tamoxifen and progestins as first- and second-line therapies respectively. Aromatase inhibitors are widely used in the neoadjuvant setting for hormone sensitive tumours and can permit subsequent breast conservation surgery when mastectomy would otherwise have been indicated. However, it is in the adjuvant setting that AI's have stimulated much interest and generated an element of uncertainty in the optimum form of adjuvant hormonal therapy for post-menopausal women with oestrogen receptor positive tumours. It seems likely that any blanket policy is no longer appropriate and a selective strategy with tailoring of therapy based on risk of relapse is the preferred option. Those patients at greatest risk of relapse may benefit most from an upfront AI whilst those with lower hazard rates for relapse may be best treated with an 'early switch' regimen involving tamoxifen for 2 – 3 years followed by an AI for a total duration of 5 years. Benefits in terms of disease-free and overall survival must be balanced against longer term adverse effects on bone health and cognitive function as well as cost. Some patients at very low risk of relapse may derive minimal additional benefit from incorporation of an AI into their treatment schedule and should receive tamoxifen only.

The three oral AI's are of comparable efficacy and are potentially interchangeable. Longitudinal studies must be undertaken with gathering of longer term data on side-effect profiles before any definitive pronouncements on clinical utility. There are particular concerns about severe oestrogen depletion amongst women receiving an AI for chemoprevention and ongoing evaluation of treatment related morbidity is essential.

INTRODUCTION

Historical Perspective

Breast cancer remains the commonest malignancy amongst women with a lifetime risk of between 10 – 12%. Almost half a million women die of the disease annually worldwide with 15,000 and 45,000 deaths per annum in the United Kingdom and United States respectively. Despite the continued rise in incidence of breast cancer, mortality rates have fallen over the past 2 decades which is attributable to a combination of screening, heightened public awareness of the disease and the introduction of adjuvant systemic therapies. Breast cancer is a predominantly post-menopausal disease in which more than three-quarters of tumours are hormone responsive. This hormone dependency of breast cancer interacts with environmental and genetic factors to determine incidence and progression of the disease. However, it is the clinical response of these tumours to hormonal manipulation

which provides a unique therapeutic opportunity in the form of targeted treatments. The latter are based on biological principles and an understanding of mammary tumourigenesis derived from pre-clinical models and *in vitro* studies of breast cancer cell lines. Interestingly, the first evidence for a direct role of oestrogens in the development of breast cancer came from the use of ablative endocrine therapies for the treatment of metastatic breast cancer. Schinzinger in 1889 suggested that breast cancer was hormonally responsive and might regress following removal of the ovaries [1]. Sir George Beatson (1896) was the first surgeon to perform such a procedure for breast cancer, reporting a favourable response to oophorectomy in a small group of pre-menopausal women with disseminated disease [2]. Surgical methods of hormonal ablation included not only oophorectomy, but also more intrusive procedures such as adrenalectomy and hypophysectomy [3]. These were associated with a higher morbidity and usually reserved as 'second line' endocrine therapies for relapse following primary ovarian suppression.

Beatson's clinical observations were made more than a century ago, and the physiological basis for regression of breast cancer was unknown at the time. Oestrogens were isolated in crystalline form in the 1930's [4] and were soon

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implicated in the initiation and promotion of mammary tumours in rodents [5,6]. The selective accumulation of radio-labelled synthetic oestrogens in target organs which responded to these hormones supported a direct role for oestrogens in normal breast development and physiology [7]. Furthermore, uptake of radiolabelled systemic oestradiol by 7,12 dimethylbenzanthracene (DMBA) – induced rat mammary tumours suggested that oestrogens may also be involved in promoting tumour growth by acting directly upon breast cancer cells *via* putative oestrogen receptors [8]. Curiously, mean plasma levels of oestrogen did not and have never been found to correlate with breast cancer risk. Moreover, administration of high dose oestrogen could lead paradoxically to regression of advanced breast cancer [9].

Oestrogen Receptors

The discovery of the oestrogen receptor consolidated understanding of oestrogen stimulated growth [10,11]. Oestrogen binding in uterine tissue of immature rats led to formulation of an early model for oestrogen mediated events in which oestrogen interacted directly with target cells *via* cytoplasmic receptors – oestrogen receptors (ER). Subsequent translocation of the ligand/receptor to the nucleus and its interaction with DNA resulted in modulation of gene transcription (oestrogen responsive genes). The uptake of tritiated oestradiol by breast tumour samples was essentially ‘all-or-none’ and this dichotomous response led to designation of tumours as ER positive or ER negative [12]. This heralded the modern era of endocrine therapy in which the clinical response of advanced breast cancer could be predicted from the ER content of metastatic lesions [13] and later of primary tumours [14]. Approximately half of all advanced breast cancers are ER positive, 60% of which will respond to hormonal manipulation compared with only 5 - 10% of ER negative tumours. Modern methods of immunoassay classify tumours as ER rich or ER poor. The Allred system has been developed to more accurately define ER expression to predict response to endocrine treatments. Tumours are assigned an intensity score (1 – 3) and a frequency score (0 - 5) and ER levels are based on an aggregate score from 0 (no expression) to 8 (strong expression) [15]. Differential responses between aromatase inhibitors and tamoxifen have been observed for lower levels of expression (0 – 3).

Anti-Oestrogens

Characterisation of the ER and its mechanism of action provided an alternative approach to hormonal manipulation. Instead of inducing a state of oestrogen deprivation by surgical intervention, the action of oestrogen could be blocked at the level of the receptor by competitive antagonism. Initial interest in sex hormone antagonists lay in their potential as oral contraceptive agents and it was the failure of tamoxifen in this capacity which ultimately changed its clinical destiny. This agent was found to block binding of oestrogen to the human ER [16]. Consistent with this ER blocking activity, tamoxifen suppressed DMBA-induced carcinogenesis in rodent mammary tumours [17,18] and inhibited growth of ER positive cancer cell lines *in vitro* [19].

Tamoxifen was first used in the treatment of advanced breast cancer [20,21] with response rates of up to 70% in

those patients expressing both ER and progesterone receptor (PR) [22] and 30% of unselected patients [23]. However, it is in the adjuvant setting that tamoxifen has found widespread application in recent years as standard hormonal therapy for large numbers of both pre- and post-menopausal women with breast cancer. It is a relatively non-toxic therapy which permits effective targeting of micrometastatic tumour foci at distant sites which are present in many patients presenting with ‘early breast cancer’. Much of the clinical success of tamoxifen is attributable not only to its effectiveness, but also its favourable side-effect profile which makes it a potential candidate for chemoprevention.

Selective Oestrogen Receptor Modulators (SERMS)

Tamoxifen is classified as an anti-oestrogen whose primary action is to competitively antagonize oestrogen at the level of cellular receptors. However, it also possesses oestrogen agonist properties on non-breast tissues such as the endometrium and bone. On the one hand, these may confer incidental benefits in terms of enhanced bone mineral density and improved lipid profiles [24,25]. On the other, this agonist activity increases the incidence of endometrial cancer and may compromise the fundamental anti-tumour activity of tamoxifen [26].

The term selective oestrogen receptor modulation or SERM encompasses this duality of action. SERM’s are non-steroidal compounds which interact with the ER and result in degrees of dimerisation of the two structurally related forms of the receptor (alpha and beta) whose distribution permits variable and tissue specific activation of oestrogen response genes. Tamoxifen is the prototype of this group of SERM’s and possesses a triphenylbutene core and basic side chain [27]. The tissue specificity results in anti-oestrogenic activity on breast tissue but partial oestrogen agonist activity on endometrium [28] and bone [29,30]. Tamoxifen modulates serum lipid profiles in an oestrogenic manner with a reduction in LDL fraction and maintenance or increase in HDL levels [31,32]. Despite a favourable modulation in the ratio of HDL/LDL cholesterol this has not been translated into a reduced incidence of ischaemic heart disease or cardiac mortality [24,25]. The configuration of the SERM-oestrogen receptor complex determines the recruitment of co-activators and co-repressors that bind to the external surface of the complex and activate oestrogen response elements [33]. The pattern of transcriptional complexes is programmed by this SERM-oestrogen receptor complex which in turn is governed by the precise chemical formula and structure of the ligand. Newer SERM’s have been developed with weaker oestrogen agonist properties and attenuated uterotrophic effects. Individual SERM’s have a clinical signature with a range of structure-activity profiles which are site specific and confer differential and non-correlative mixed agonist/antagonist activity between species and tissues [27].

Newer SERM’s with attenuated uterotrophic activity together with selective oestrogen receptor downregulators (SERD’s) are under development and evaluation. Nonetheless, approaches to endocrine manipulation have shifted away from directly targeting the ER, to inducing states of oestrogen deprivation in post-menopausal women, using highly selective oral aromatase inhibitors which do not affect

Table 1. Summary of the 3 Principle Third Generation Aromatase Inhibitors

	ANASTROZOLE	LETROZOLE	EXEMESTANE
Type (1 or 2)	2	2	1
Chemical structure	<i>triazole (non-steroidal)</i>	<i>triazole (non-steroidal)</i>	<i>androstenedione analogue</i>
Binding to enzyme	<i>reversible</i>	<i>reversible</i>	<i>irreversible</i>
Site of enzyme binding	<i>p450 haem site</i>	<i>p450 haem site</i>	<i>steroid binding site</i>
Reduction in enzyme activity/ Circulating oestrogen levels	>98%	>98%	>98%
Mode of administration	oral	oral	oral

adrenal synthesis of glucocorticoids and mineralocorticoids. These are emerging as a new class of hormonal therapies which are at least as effective as and possibly superior to tamoxifen for treatment of metastatic breast cancer and are challenging the primacy of tamoxifen in the adjuvant setting. Furthermore, aromatase inhibitors appear to have a greater impact on the incidence of contralateral breast cancer than tamoxifen and are being evaluated in the chemopreventive setting (IBIS II). Though these agents are associated with fewer thromboembolic events [34], there are potential adverse effects from longer term oestrogen deprivation, including bone loss and impaired cognition [35].

This article will discuss the indications for use of aromatase inhibitors in various stages of breast cancer including neoadjuvant schedules and chemoprevention. Emphasis will be placed on trial data and recommendations based on comparative efficacy, toxicity and cost.

Mechanism of Action of Aromatase Inhibitors

Following cessation of ovarian function at the menopause, the principle source of oestrogens are from peripheral synthesis in adipose tissue and the adrenal glands. The enzyme oestrogen synthetase or aromatase is present within these tissues together with skeletal muscle and two-thirds of breast tumours [36]. This cytochrome p450 enzyme converts the androgens testosterone and androstenedione to oestradiol and oestrone respectively. This process of aromatization in peripheral tissues releases relatively small amounts of oestrogen into the general circulation compared with ovarian sources in pre-menopausal women. However, local concentrations of oestrogen within the post-menopausal breast can reach levels comparable to the pre-menopausal state due to local production by breast adipose tissue supplemented by intra-tumoural aromatase activity [37].

Aromatase inhibitors block peripheral aromatization of androgens and reduce both serum and intra-mammary tissue levels of oestrogen and have therapeutic efficacy in post-menopausal women only. When ovarian function remains intact, aromatase inhibitors can produce a reflex increase in levels of GnRH (luteinising hormone/follicle stimulating hormone) which in turn will stimulate the ovaries and can lead to supra-physiological levels of oestrogen in premenopausal women. Use of GnRH antagonists in conjunction with aromatase inhibitors are currently being investigated as a possible strategy for hormonal manipulation in younger pre-

menopausal women who are strongly ER positive (Austrian Breast Cancer Study Group 12; TEXT trial) [38].

All of the 'third-generation' aromatase inhibitors share the convenience of being once daily oral preparations with low toxicity and are classified as TYPE 1 or TYPE 2 depending on their mechanism of action. The three main agents in current clinical usage are exemestane, anastrozole and letrozole (Table 1). The former is a steroidal analogue of androstenedione which binds *irreversibly* to the steroid binding site of the enzyme with inactivation and destruction of the enzyme. By contrast, the latter two agents are non-steroidal compounds (triazoles) which bind *reversibly* to the p450 component of the haem site.

Despite differing mechanisms of action, both type I and II aromatase inhibitors reduce enzyme activity and circulating levels of oestrogen by more than 98% [39]. *In vitro* studies with a variety of cell systems (including breast cancer cell lines) suggest that letrozole is more than 10 fold potent than anastrozole at inhibiting aromatization [40]. Moreover, letrozole induces a more profound decrease in whole body aromatization and levels of plasma oestrogen (estrone [E1], oestrone sulphate [E1S]) in post-menopausal breast cancer patients than anastrozole [41]. These differences in the pharmacodynamic profiles of these two agents has not translated into any gains in time to progression (TTP) for letrozole in the context of metastatic breast cancer and their clinical relevance remains uncertain [42].

Aromatase Inhibitors in Advanced Breast Cancer

Treatment of metastatic breast cancer with tamoxifen prolongs TTP and improves overall quality of life. A high proportion of patients who initially respond to tamoxifen in this palliative setting eventually acquire resistance [43]. Aromatase inhibitors have shown not only superior efficacy, but also better tolerability compared to second-line hormonal therapies such as progestins and aminoglutethimide with response rates ranging from 8 – 24% [44].

Three seminal studies have examined the use of aromatase inhibitors as first-line therapy for advanced breast cancer. Two initial randomized trials compared anastrozole with tamoxifen in post-menopausal women with ER positive and/or PgR positive or receptor unknown advanced breast cancer [34,45]. In the North American trial, 353 patients were randomly allocated either tamoxifen (20mg/day) or anastrozole (1mg/day) as first line treatment [34] whilst al-

most twice this number of patients were randomized to receive similar treatment schedules in the European trial [45]. Though the North American trial showed a statistically significant ($p=0.005$) improvement in TTP with an aromatase inhibitor (11.1 months versus 5.6 months), a combined analysis suggested comparable efficacy and anastrozole was recommended as an alternative to tamoxifen as first line treatment of advanced breast cancer in post-menopausal women [46]. Though the North American trial showed an improvement in TTP, there was no difference in objective response rates nor overall survival [34]. By contrast, the larger European study showed no difference in any of these endpoints with an average TTP of 8 months for the two treatment groups. It is noteworthy that in the North American trial, nearly all patients had documented hormonal status compared with only half those in the European trial. It therefore seems likely that the receptor unknown group contained a greater number of hormone receptor negative tumours. A third study randomized over 900 patients with hormone receptor positive or unknown receptor status advanced disease to either tamoxifen or letrozole. This particular aromatase inhibitor was found to be superior to tamoxifen as first line treatment in terms of TTP (letrozole 9 months versus tamoxifen 6 months; HR 0.70, 95% CI 0.60 – 0.82 $p > 0.0001$) and the secondary endpoints time to treatment failure (TTF) and overall objective tumour response rates (letrozole 32% versus tamoxifen 21%; $p < 0.001$). Interestingly, a cross-over policy was adopted to evaluate effects of sequencing on overall survival and no significant differences were found for patients crossing from letrozole to tamoxifen and vice versa. However, in an exploratory analysis of patients who did not cross over to the other drug, letrozole conferred a statistically significant overall survival benefit of 14 months. Furthermore, the benefits from aromatase inhibitors in terms of TTP, TTF and response rates were evident in all patient subgroups ($p < 0.05$) [47]. Fewer than 20% of patients had received prior tamoxifen in this study of Mourisden and colleagues, but 39% and 22% of patients had received this treatment in the North American and European trials evaluating anastrozole [34,45]. Aromatase inhibitors may be of value as first line treatment of advanced disease in patients who have previously received adjuvant tamoxifen and are therefore less likely to respond to this agent in the metastatic setting [48].

Favourable outcomes have also been reported for the aromatase inhibitor exemestane as first line treatment for advanced disease [49]. A phase III study involving 400 patients with hormone receptor positive metastatic breast cancer compared tamoxifen (20mg/day) with exemestane (25mg/day) [49]. Response rates were higher in the aromatase inhibitor group (exemestane 45% versus tamoxifen 31%; $p = 0.005$) at a median follow up of 29 months. TTP was longer for exemestane (9.9 months versus 5.8 months) but neither this endpoint nor overall survival were statistically different.

A pooled analysis of eight prospective randomized studies involving 1615 patients treated with an aromatase inhibitor (letrozole, anastrozole, fadrozole, formestane or exemestane) and 1623 with tamoxifen for metastatic breast cancer has recently been presented [50]. Despite considerable heterogeneity amongst these trials, the hazard rate for risk of

TTP for aromatase inhibitors compared with tamoxifen was 0.83 ($p < 0.001$). When confined to non-steroidal aromatase inhibitors, the HR was 0.79 ($p < 0.001$). Overall response rates were higher for aromatase inhibitors (relative risk 1.18; $p < 0.01$) but no difference in overall survival emerged from this pooled analysis. However, failure to demonstrate an overall survival advantage may partially be attributable to the confounding effects of chemotherapy which many ER positive post-menopausal women have received. The safety profile of aromatase inhibitors in terms of thromboembolic events was superior and this echoes findings from the study of Mourisden in respect of anastrozole. This coupled with a lower incidence of vaginal bleeding (relative risk 0.36; $p < 0.01$) is an important factor in assessing the risk:benefit ratio for aromatase inhibitors particularly in the adjuvant and chemopreventive settings [50].

Neoadjuvant Therapy with Aromatase Inhibitors

By analogy with neoadjuvant chemotherapy, hormonal treatment can be used pre-operatively with the intention of downstaging tumours. This may render inoperable tumours operable and permit breast conservation in patients who might otherwise require mastectomy [51,52]. Hormonal therapies are less toxic and potential side-effects of chemotherapy can be avoided in elderly patients and those with a poor performance status. Furthermore, patients with hormone receptor positive disease are less likely to achieve a complete pathological tumour response from pre-operative chemotherapy schedules [53]. The aromatase inhibitors have consistently outperformed tamoxifen in the neoadjuvant setting, when endpoints include not only response rates, but also breast conservation rates [54,55].

In a study of 337 patients with hormonally responsive (ER/PR positive) locally advanced and inoperable breast cancer, letrozole (2.5mg/day) administered as a pre-operative schedule for 4 months yielded significantly better response rates compared with tamoxifen (20mg/day) given for a similar period (55% versus 36% respectively; $p < 0.001$) [54]. The difference in sonographic response rates were less dramatic (35% versus 25%; $p = 0.042$). A significantly higher proportion of those in the letrozole group were suitable for breast conservation after induction hormonal treatment (45% versus 35% respectively; $p = 0.022$).

The IMPACT study (Immediate Preoperative Arimidex, Tamoxifen or Combined with Tamoxifen) [55] randomized 330 patients with operable hormone responsive breast cancer to 3 months of anastrozole alone, tamoxifen alone or a combination of the two. The objective clinical response rates in the 3 groups were 37.2%, 36.1% and 39.4% respectively. Though these response rates were not significantly different, anastrozole was more effective at downstaging tumours to permit breast conservation surgery (BCT) according to surgeon assessment (46% considered suitable for BCT after anastrozole versus 22% for tamoxifen; $p = 0.03$). However, there was no significant difference in breast conservation rates when analysed on the basis of actual surgery performed at 3 months (44% versus 31% respectively; $p = 0.23$). Despite higher response rates for letrozole compared with anastrozole in the neoadjuvant setting (55% versus 37.2%), treatment of primary, operable ER positive tumours with

letrozole or anastrozole for 2 weeks results in similar changes in the proliferation marker Ki67 [56]. Anastrozole and exemestane have been reported to induce comparable clinical and pathological responses to 4 cycles of doxorubicin/paclitaxel in hormone receptor positive tumours. Moreover, low dose oral cyclophosphamide (50mg daily) in combination with letrozole provides no additional clinical benefit over letrozole alone in older patients (>60 years) with ER positive breast cancers [57]. There is some evidence for a preferential decrease in mean Ki67 levels in ER positive/HER2 negative patients receiving 3 – 4 months of pre-operative letrozole. A significant fall in mean Ki67 levels was found in HER2 negative patients but levels remained unaltered in HER2 positive patients ($p < 0.0001$) [58].

These results suggest that HER2 positive patients may more readily develop resistance to aromatase inhibitor therapy [58]. Inhibition of HER 2 over-expression in tumour xenografts with a combination of gefitinib, trastuzumab and pertuzumab (GTP) can restore or increase ER expression thus overcoming endocrine resistance and allowing further hormonal manipulation [59]. Combinations of aromatase inhibitors with epidermal growth factor and tyrosine kinase inhibitors are providing promising data in pre-clinical and some clinical studies [60].

Aromatase Inhibitors as Adjuvant Treatment

Tamoxifen has been the mainstay of adjuvant systemic hormonal treatment of breast cancer for the past 20 years. Though there is extensive data confirming the clinical efficacy of tamoxifen in prolonging both disease-free and overall survival, its dominance is being challenged by the emergence of the oral aromatase inhibitors which may combine greater efficacy with a more favourable side-effect profile (particularly in terms of thromboembolism and endometrial cancer). Use of aromatase inhibitors in the adjuvant setting is being investigated with two principle approaches – head to head and sequencing trials with an early or late switch. Before discussing the 4 main phase III randomized trials in more detail, it is helpful to review the data supporting the use of tamoxifen as adjuvant therapy for early stage breast cancer.

Adjuvant Tamoxifen

The series of overviews by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) [61] undertaken at 5 yearly intervals have confirmed that tamoxifen reduces rates of local relapse and improves overall survival. The most recent analysis involving 37,000 patients reveals benefits for all age groups irrespective of menopausal and nodal status. At least 5 years of tamoxifen therapy confers a proportional reduction in mortality of 26% and up to 47% reduction in local recurrence at 10 year follow up. These benefits are confined to patients with ER positive tumours, though the number of patients with ER negative tumours was small with fewer events. When ER negative tumours were excluded from the analysis, absolute risk reductions for local recurrence were 14.9% for node negative patients and 15.2% for node positive patients ($p < 0.001$). Absolute mortality reductions for node negative and node positive groups were 5.6% and 10.9% respectively ($p < 0.0001$).

The NSABP B-14 trial re-randomised node negative patients who remained disease-free after 5 years of adjuvant tamoxifen to a further 5 years of the same or placebo. This revealed no further reduction in disease recurrence nor improvement in longer term survival [62]. Tamoxifen is a cytostatic agent and there is a theoretical rationale for extended adjuvant endocrine treatment. However, the survival benefits of tamoxifen continue beyond 5 years although much of the effect on recurrence occurs before cessation of tamoxifen treatment [63]. This carry-over effect is clinically opportune and of particular importance in the context of the B-14 trial results which fail to reveal any benefit from more prolonged tamoxifen therapy. Furthermore, this study showed no statistically significant reduction in contralateral breast cancers following the second randomization. Continued therapeutic intervention may not impart any overall survival gain with respect to either the primary tumour or contralateral breast cancer. In the case of 10 years of tamoxifen, a net detrimental effect may ensue from adverse side-effects such as increased thromboembolism and gynaecological problems. Indeed, the most recent analysis of the B-14 trial shows a significantly shorter disease-free and overall survival for those patients treated for 10 years. These results should be contrasted with those from the MA-17 trial (see below) in which extended treatment beyond 5 years with an aromatase inhibitor yielded an overall survival improvement for node positive patients [64].

Adjuvant Trials

Adjuvant trials of aromatase inhibitors have investigated third-generation oral agents using a variety of schedules, including head to head comparisons of tamoxifen versus and aromatase inhibitor, aromatase inhibitors in combination with tamoxifen and early sequencing with a switch to an aromatase inhibitor after 2 – 3 years of tamoxifen (Fig. 1). The MA-17 trial specifically addressed the issue of extended adjuvant therapy and the BIG 1-98 trial [65] incorporated an inverse early switch arm of an aromatase inhibitor for 2 – 3 years followed by tamoxifen.

1) Head To Head Trials

a) *ATAC trial* - the ATAC (Arimidex, Tamoxifen, Alone or in Combination) study is the largest of the these adjuvant trials and was the first to publish results [66]. More than 9000 patients were enrolled in the original 3 way randomization. Following primary loco-regional treatment post-menopausal women were randomized to receive tamoxifen alone, anastrozole alone or a combination of the two drugs for a total of 5 years. The rationale for the combination arm was based on differing mechanisms of action for tamoxifen and anastrozole which were thought to be potentially synergistic. However, the combination arm was subsequently abandoned due to lack of any additional efficacy compared to tamoxifen alone with further evaluation confined to the monotherapy arms where 6186 patients received one or other agent. Early results of this trial at a median follow up of 33 months [66] revealed a statistically significant benefit for anastrozole over tamoxifen in terms of local recurrence (disease-free survival), time to recurrence and incidence of contralateral breast cancer. This initial analysis also demonstrated significant advantages for anastrozole in respect of

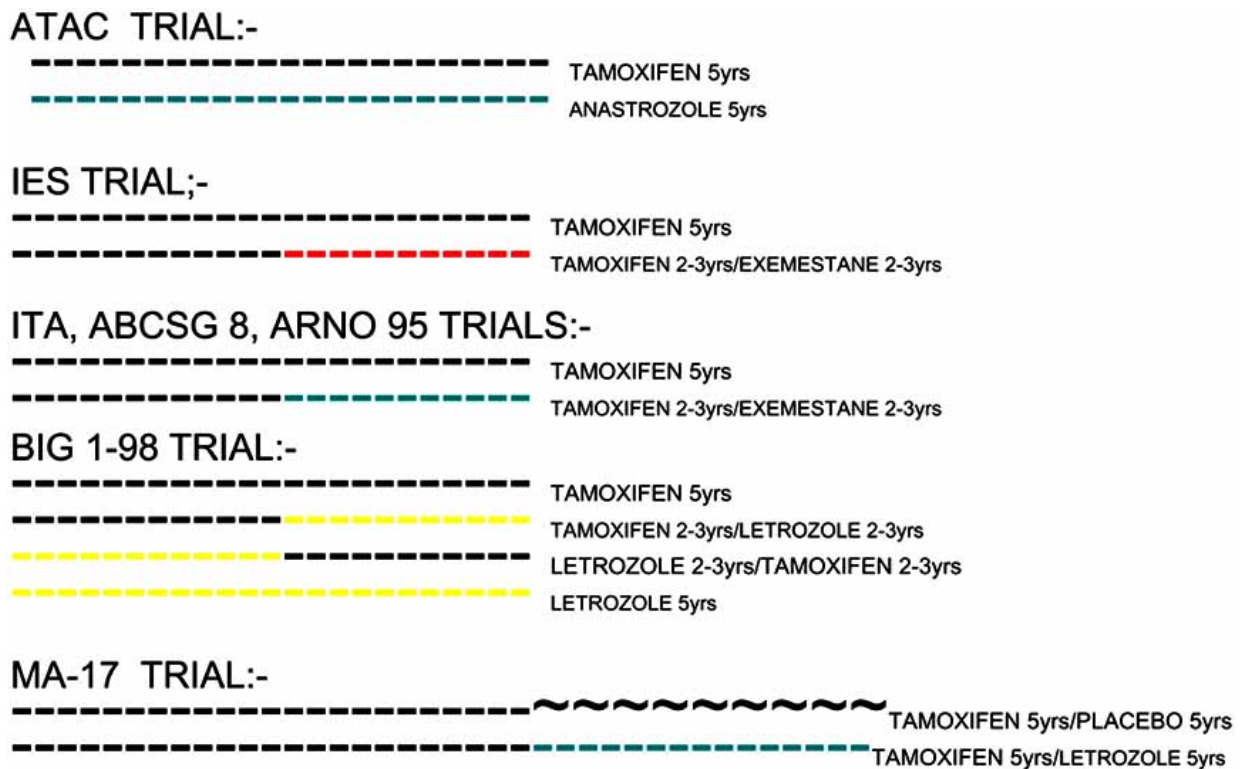


Fig. (1). Adjuvant hormonal therapy trials with aromatase inhibitors.

treatment related side-effects, which included serious adverse events such as endometrial cancer and thromboembolism. The most recent update of this trial provided data at 68 months follow up [67]. This showed a continuing divergence of the curves for disease-free survival with evidence of a carry-over effect and a reduction in time to distant recurrence in favour of anastrozole. In hormone receptor positive patients, anastrozole increased disease-free survival by 17% (HR 0.83 95% CI 0.73 – 0.94; $p = 0.01$) representing an absolute risk reduction of 2.5% at 5 years. Though there was a reduction in distant disease-free survival (HR 0.93 95% CI 0.80 – 1.07), this was not significant and no overall benefit was apparent for overall survival (HR 0.97 95% CI 0.85 – 1.12). There was a relative reduction of 53% in the incidence of contralateral cancers in hormone receptor positive patients (26 in anastrozole group versus 53 in tamoxifen group).

There is evidence from a limited subgroup analysis of the ATAC trial that patients with ER positive but PgR negative tumours and those with over-expression of HER2-neu may derive proportionately greater benefit from anastrozole (HR 0.48) [68]. However, this contrasts with results for letrozole within the BIG 1-98 study (see below).

The ATAC Trialists Group have recently published a comprehensive side-effect profile of anastrozole and tamoxifen within the context of the ATAC trial [69]. Fewer than 10% of patients remained on trial treatment at the time of analysis and all of these had less than 12 months scheduled treatment remaining. Data were analysed with stringent statistical criteria (99% CI) and a p -value of <0.01 for significance level (non-predefined events). Results reinforced previous findings that anastrozole is associated with lower

rates of thromboembolism (2.8% versus 4.5%; $p = 0.0004$), uterine malignancy (0.22% versus 0.76%; $p = 0.02$) and cerebrovascular events (2.0% versus 2.8%; $p = 0.03$) but similar rates of cardiovascular morbidity (ANGINA 2.3% versus 1.6%; $p = 0.07$, MYOCARDIAL INFARCTION 1.2% versus 1.1%; $p = 0.7$). Though the annual fracture rate was higher in the anastrozole group, this has not increased over time and the excess fractures appear confined to the axial skeleton and upper limbs. Of note, the incidence of hip fractures was similar (and relatively low) for both groups which is a reassuring finding bearing in mind the clinical and economic impact of fractures at this site within the general population. Thus with more prolonged follow up further adverse events have not occurred in the anastrozole group and statistical significance has been maintained for the more favourable differences in pre-defined side-effect categories.

b) *BIG 1-98 trial* - the Breast International Group (BIG) 1-98 trial was originally intended to be a head to head study comparing 5 years of tamoxifen with 5 years of upfront letrozole in a similar design to the monotherapy arms of the ATAC trial. Shortly after commencement in March 1998, the trial protocol was amended to incorporate two additional early switch arms. Thus patients would be treated initially with tamoxifen for 2 years, then changed to letrozole for 3 years or vice versa (2 years letrozole followed by 3 years of tamoxifen). Approximately three-quarters of the 8028 patients within this trial were accrued after introduction of these switching arms. Furthermore, randomization was undertaken at the start of adjuvant therapy and not at the time of switching. All patients had hormone receptor positive disease (60% ER positive/PgR positive; 20% ER positive/PgR negative) and 40% were node positive which is a

similar proportion to the ATAC trial). Results of this trial were presented in St Gallen in January 2005 as a primary core analysis (8010 patients) [65]. Upfront letrozole was compared with tamoxifen and the analysis included patients from all 4 arms of the trial. However, for those patients in the sequential arms, the analysis excluded events beyond the point of switching. At a median follow up of 25.8 months, letrozole was found to significantly improve disease-free survival by 19% (HR 0.81 95% CI 0.70 – 0.93; $p = 0.003$) representing an absolute risk reduction of 2.6%. In contrast to anastrozole in the ATAC study, the improvement in time to distant metastases was statistically significant (HR 0.73 95% CI 0.60 – 0.88; $p = 0.001$). There was no significant difference in overall survival, but the risk reduction was 14% (HR 0.86 95% CI 0.70 – 1.06; $p = 0.16$) compared with 3% for anastrozole in the ATAC study. Of note, the improvement in disease-free survival was independent of PgR status and prior chemotherapy (approximately 25% of patients). Moreover, there was centralized review of ER/PgR status within the BIG 1-98 trial. The side-effect profile of letrozole was similar to anastrozole with a reduction in risk of thromboembolism and uterine malignancy (odds ratio 0.40; $p = 0.078$). However, there was a significant increase in the fracture rate amongst patients receiving letrozole (odds ratio 1.44; $p = 0.0006$) and though hypercholesterolaemia was more common in the letrozole group, there was no significant difference in the incidence of severe cardiovascular events. A head to head comparison between letrozole and anastrozole in node positive patients with early breast cancer is being undertaken in the Femara versus Anastrozole Clinical Evaluation (FACE) trial.

2) Early Switch Trials

Though data is eagerly awaited from the switch arms of the BIG 1-98 trial, results from several other trials which specifically compare 5 years of tamoxifen with 2 – 3 years tamoxifen followed by 2 – 3 years of an aromatase inhibitor are available. These are much smaller trials than ATAC or BIG 1-98, though collectively involve large numbers of patients. Furthermore, some of these randomize immediately after primary surgery, whilst others randomize at the time of switching.

The relevant switch trials are listed below:-

- a) INTERGROUP EXEMESTANE (IES) TRIAL (4742 patients)
- b) ITALIAN (ITA) TRIAL (448 patients)
- c) AUSTRIAN TRIALS (ABCSG 8 and ARNO 95) (448 patients)

The IES trial will be discussed first [70], followed by the remaining 3 trials involving a switch from tamoxifen to anastrozole which have been amalgamated into a recent meta-analysis [71].

a) *Intergroup Exemestane (IES) trial* - the IES trial involved almost 5000 women with early stage breast cancer who were randomized after 2 – 3 years of tamoxifen to either switch to exemestane (2,352 women) or continue with tamoxifen (2,372 women) for a total period of 5 years. The median duration of tamoxifen therapy prior to randomization was 2.4 years. All patients had hormone receptor positive

tumours or unknown receptor status and approximately 50% were node positive. Those unknown patients subsequently found to be ER negative were excluded from the analysis. Switching to exemestane after 2 – 3 years of tamoxifen significantly improved disease-free survival compared with 5 years of tamoxifen. At a median follow up of 4.8 years, the risk of relapse was reduced proportionately by 26% (HR 0.74 95% CI 0.64 – 0.85; $p < 0.0001$). The benefit for exemestane in terms of overall survival just reached significance (HR 0.83 95% CI 0.69 – 0.99; $p = 0.04$) when the analysis was confined to ER positive and ER unknown patients rather than all patients on an intention to treat basis. This is the first adjuvant trial to show a gain in overall survival for use of an aromatase inhibitor within the usual treatment span of 5 years. The trial also revealed a 44% reduction in incidence of contralateral breast cancer.

There were significantly fewer thromboembolic ($p = 0.006$) and serious gynaecological events ($p < 0.001$) in the exemestane group but a non-significant increase in fracture rate. There were no statistically significant differences in the incidence of myocardial infarction, angina or cerebrovascular accidents between the two groups [72].

b) *Italian (ITA) [73] and Austrian trials (ABCSG 8 and ARNO 95) [74]* - each of these three individual trials have investigated an early switch (2 – 3 years) from adjuvant tamoxifen to anastrozole in post-menopausal women with hormone responsive breast cancer. The design of these trials was broadly similar and addressed the same question. This formed the basis and justification for a meta-analysis performed by Jonat and presented at the San Antonio Breast Cancer Symposium in 2005 [71]. There was some lack of heterogeneity and certain key differences between the trials which are summarized in Table 2. Some of the trials randomized patients at the start of adjuvant systemic hormonal treatment (i.e. immediately after surgery) whilst others randomized after 2 – 3 years of tamoxifen (i.e. at the time of switching). There was also variation in the stage distribution of patients and in particular the proportion of node positive patients and hence the absolute risk of relapse. Despite these limitations, combined group analysis was employed using raw data rather than processed results of individual trials. A

Table 2. Summary of Patient Characteristics in Early Switch Trials of Tamoxifen and Anastrozole Used for Meta-Analysis [75]

ITALIAN (ITA) TRIAL (448 pts)
99% patients node positive
grade III tumours included
- >50% patients underwent mastectomy
ABCSG 8 TRIAL (2262 pts)
- randomised immediately after surgery (not at point of switching)
- grade I and II tumours
- 25% node positive
- 80% breast conservation
ARNO 95 (962 pts)
- similar to ABCSG 8 but patients randomised at time of
- switching to anastrozole

previous combined analysis of the Austrian trials showed that switching to anastrozole after 2 years of tamoxifen therapy significantly improved event-free survival at a median follow up of 28 months (HR 0.60 95% CI 0.44 – 0.80; $p = 0.0009$) [74].

The meta-analysis of the 2 Austrian trials combined with the Italian trial involved a total of 4006 patients of whom 2009 switched from tamoxifen to anastrozole and 1997 remained on tamoxifen for 5 years. The median follow up across all trials was 30 months and incorporated 10,000 person years. The principle aim of the meta-analysis was to determine whether improvements in event-free survival translate into benefits in long term outcomes (overall survival). For each therapy arm, the distribution of event-free and overall survival was estimated using the Kaplan-Meier technique. The results showed a statistically significant disease-free survival advantage for switching from tamoxifen to anastrozole (HR 0.59 ; $p = 0.001$). In particular, there was a significant improvement in overall survival with a 29% reduction in risk of death from breast cancer (HR 0.71; $p = 0.038$). A Forest plot of individual trials revealed that improvement in survival only reached significance in the ARNO 95 trial [75]. Analysis of the ABCSG 8 trial alone at a median follow up of 30 months showed that switching to anastrozole after 2 years of tamoxifen significantly reduced the incidence of local events. The magnitude of the risk reduction was greater when analysed from the point of switching (40%) compared with the time of randomization, which included the first 2 years of tamoxifen (24%). Furthermore, the disease-free survival advantage for switching from tamoxifen to anastrozole was lost when the analysis was done from the time of randomization ($p = 0.07$) rather than at therapy switch ($p = 0.01$) [76]. However, there was no overall survival advantage (HR 0.93 ; $p = 0.726$). The authors concluded from this meta-analysis that switching from tamoxifen to anastrozole after 2 – 3 years results in a) fewer recurrences b) benefits in terms of overall survival and c) favourable safety profiles. It was recommended that post-menopausal patients with hormone responsive breast cancer should be switched to anastrozole upon completion of 2 – 3 years of tamoxifen treatment. The methodology employed for this meta-analysis has been questioned and the lack of homogeneity is of some concern. Moreover, the ARNO 95 and ITA trials are relatively small compared with the ABCSG 8 trial and have correspondingly fewer events.

An element of uncertainty now prevails over the optimum form of adjuvant endocrine therapy for post-menopausal women with hormone receptor positive tumours. This has been generated by emerging data from the above trials and clarification is now demanded on how best to advise and manage patients who are newly diagnosed with breast cancer or have already received some years of tamoxifen [77]. The American Society of Clinical Oncology Technology Assessment recommends that adjuvant hormonal therapy for this group of patients should include an aromatase inhibitor prescribed either as initial therapy or sequenced after tamoxifen for 2 – 3 years (early switch) or 5 years duration [78]. It is implicit from this consensus that 5 years of tamoxifen alone is no longer considered adequate therapy for any group of post-menopausal oestrogen receptor positive patients. This statement represented a major shift in

management strategy for breast cancer patients and was taken one step further in a paper published on behalf of the ATAC Trialists Group [67]. This advocated that not only should 5 years of an aromatase inhibitor upfront be the preferred hormonal option for these women, but that anastrozole should be the agent of choice. Such conviction was not, and is still not justified at the present time in the face of alternative and potentially interchangeable aromatase inhibitors. The persistent price differential with tamoxifen will inevitably influence any cost:benefit analysis.

The IES trial is the only adjuvant study to show an overall survival advantage for use of an aromatase inhibitor within the conventional 5 year treatment span. These latest results from the IES trial [72] taken together with those of the Austrian (ABCSG 8/ARNO 95) [74] and Italian (ITA) [73] studies (including the above meta-analysis) suggest that an early switch policy might be the most efficacious approach. The proportional risk reductions for disease-free survival are greater within the early switch than head to head comparisons of tamoxifen and an aromatase inhibitor. The definitive results of the BIG 1-98 study will be available in 2008 and this relatively large trial will provide important data on the relative benefits of upfront letrozole versus an early switch from tamoxifen after 2 – 3 years (or *vice versa*).

It seems likely that any blanket policy for adjuvant hormonal therapy in post-menopausal women with early breast cancer is no longer appropriate. A selective strategy based on risk of relapse may prove optimal [77]. There is evidence that patients with ER positive but PgR negative tumours and those with over-expression of HER2 neu may derive proportionately greater benefit from aromatase inhibition [68] with a risk reduction for local relapse in excess of 50%. However, there is conflicting data on this issue and in the analysis of the BIG 1-98 trial, letrozole was as effective in patients with ER positive/PgR positive tumours as those with ER positive/PgR negative tumours [65]. There are problems with standardization and quality of assays for PgR measurements and the BIG 1-98 study was the only trial in which central review of hormonal status was undertaken. Progesterone receptor negative tumours have higher rates of proliferation and aneuploidy and may be correlated with HER2 neu expression [79]. Letrozole is effective in HER2 positive disease and also those patients with relatively poor hormone receptor expression.

Extended Adjuvant Endocrine Treatment

The above adjuvant trials have examined the use of aromatase inhibitors within the usual treatment span of 5 years. Though more than three-quarters of recurrences occur within the first 5 years, late relapses do occur and are more common in hormone receptor positive women who have completed 5 years of adjuvant tamoxifen therapy [80]. Though there is a rationale for continued adjuvant therapy beyond 5 years, an additional 5 years of the same agent i.e. tamoxifen confers no gain in either disease-free or overall survival [62]. Aromatase inhibitors offer the opportunity for extended adjuvant therapy using a different agent with a different mechanism of action.

1) *MA - 17 trial* - this trial randomized 5187 patients who were disease-free upon completion of 5 years standard ta-

moxifen therapy to either letrozole (2.5mg per day) or placebo for a further 5 years. All patients had started letrozole within 3 months of stopping tamoxifen. An interim analysis was carried out and published in October 2003 at a median follow up of 30 months when the number of events had exceeded a pre-determined figure (171). These initial results showed a significant improvement in disease-free survival for those patients receiving extended adjuvant therapy with letrozole (HR 0.58 95% CI 0.45 – 0.75; $p = 0.0004$). In addition to a reduction in risk of recurrence by 42%, there was also a statistically significant decrease in distant metastases and an increase in overall survival in the node positive group (HR 0.61 ; $p = 0.04$). An updated analysis of this trial established letrozole as the first aromatase inhibitor to improve outcome after completion of 5 years tamoxifen therapy [81]. Indeed, the treatment effect was so strong that the trial was unblinded and letrozole was licensed for use as extended adjuvant endocrine therapy. The trial received some notoriety due to this early unblinding with patients in the placebo arm being offered letrozole for ethical reasons. Amongst the 2268 patients originally in the placebo arm, 1655 opted to switch to letrozole. The other 613 patients within the placebo group declined letrozole and remained on placebo. An analysis of this trial post-unblinding revealed a significant improvement in several endpoints for women who switched to letrozole compared with continuation of placebo [82]. These included a) disease-free survival (HR 0.31 ; $p < 0.001$) b) distant disease-free survival (HR 0.28 ; $p < 0.002$) and c) overall survival (HR 0.53 ; $p < 0.05$). There was also a further reduction in contralateral breast cancer (HR 0.23 ; $p < 0.012$). Thus extended adjuvant endocrine treatment with letrozole can improve outcomes even when commenced after a period off adjuvant hormonal therapy. However, this post-unblinding analysis was not based on randomized data and clearly the two arms were not balanced for patient and tumour characteristics. Those patients who were switched from placebo to letrozole were more likely to be younger patients with more aggressive node positive tumours and treated with prior chemotherapy. Thus the group who switched to letrozole from placebo had a greater risk of relapse and a worse prognosis which has been cited as justification for the decision to unblind. Goss has emphasized that breast cancer patients remain at chronic risk of relapse and reintroduction of endocrine therapy at any point along the pathway will improve outcome. Dormant cancer cells can be activated or 'kick started' many years after primary treatment of breast cancer. Hazard rates have been examined for recurrence in the setting of extended adjuvant endocrine treatment within the MA-17 trial [83]. A non-parametric kernel smoothing method was used to estimate hazard ratios at various time points. Trends in hazard ratios over time were assessed using a Cox model with time dependent co-variables. The results showed that hazard rates for disease recurrence were higher for the placebo group after discontinuing tamoxifen and increased with time. This implies that there is a residual risk of recurrence in patients completing 5 years of tamoxifen therapy. For those patients on letrozole, the hazard rate peaked at 2 years and then fell. The hazard ratio for recurrence (letrozole:placebo) showed a trend to decrease over time and there was greater benefit from letrozole with more prolonged therapy [83].

2) *MA – 17R trial* - trials are ongoing investigating the benefit of more extended adjuvant therapy of up to 15 years. In the MA-17R trial patients are re-randomised after completion of 5 years letrozole (10 years of endocrine treatment in total) to either another 5 years of letrozole or placebo. However, with these supra-extended treatment periods, consideration must be given to side-effects and quality of life issues as well as cost. In the post-unblinding analysis of the MA-17 trial, letrozole was generally well tolerated but there were symptoms of oestrogen deprivation with an increased incidence of newly diagnosed osteoporosis ($p = 0.007$), but a non-significant increase in fracture rate. There were no differences in cardiac morbidity between the 2 arms.

Chemoprevention of Breast Cancer

Recent trials have established the principle of chemoprevention and confirmed that the SERM tamoxifen can reduce the incidence of breast cancer. However, a decrease in disease specific mortality has not yet been demonstrated and it remains unclear whether tamoxifen will ultimately improve mortality or merely delay onset of the disease. Adjuvant trials have shown that at least 5 years of tamoxifen therapy can reduce the incidence of contralateral breast cancer by 47% [61]. The largest of the 3 seminal chemoprevention trials (NSABP – P1) has revealed a reduction in the cumulative incidence of both invasive and non-invasive cancer by 49% ($p = 0.0001$) and 50% ($p < 0.002$) respectively [84]. Initial analyses of the smaller European studies showed that 5 years of tamoxifen conferred no chemoprotective effect [85,86] and a recent follow up of the Italian study reinforces earlier conclusions that tamoxifen does not significantly reduce the incidence of breast cancer in hysterectomised women at usual or slightly reduced risk of the disease [87].

The IBIS I trial involved the double-blind randomization of 700 healthy women at increased risk of breast cancer to either 5 years of tamoxifen therapy or placebo. Tamoxifen reduced the incidence of breast cancer by one-third and combined analysis of all chemoprevention trials have shown an overall reduction of 38% in the incidence of invasive and non-invasive malignancy [88]. These trials have highlighted the dilemma of administering a chemopreventive agent to healthy women which not only has significant side-effects but may also lead to an increase in all-cause mortality. In the latest analysis of chemoprevention trials by Cuzik, thromboembolism was a relative contributor to non-breast cancer deaths, with two possible deaths from pulmonary embolism in the tamoxifen arm of the IBIS study. The risk:benefit ratio for tamoxifen is shifted in the chemopreventive setting, where otherwise healthy women receive a pharmacological intervention for which the benefits are less tangible. The absolute benefit for an individual woman must be balanced against risks of endometrial cancer and thromboembolic phenomena, together with other side-effects such as hot flashes, sexual dysfunctioning and cataracts [89]. Healthy women may be affected with life-threatening conditions when they may never have developed breast cancer. It was this strong desire to minimize side-effects which spurred the STAR trial, a head to head comparison of tamoxifen with raloxifene as chemopreventive agents. Like tamoxifen, raloxifene is a triphenylethylene and classified as a SERM. It had been found to be associated with an incidental risk re-

duction of more than 77% for breast cancer in the MORE trial for osteoporosis [90]. This trial recruited patients with osteoporosis and no family history of breast cancer. The STAR trial specifically aimed to evaluate the risk:benefit ratio for these two agents, but some have commented that the trial is comparing "apples and pears". Initial results have shown that raloxifene is similar to tamoxifen in reducing the incidence of invasive breast cancer by 50% (statistically equivalent; 167 versus 163 cancers respectively). However, it appears to have little effect on non-invasive forms of the disease, suggesting that raloxifene may interfere with the progression of in situ to invasive disease, but have no impact on pre-malignant to in situ transition [91].

In terms of side-effects, raloxifene is at best moderately superior to tamoxifen and at worse of marginal statistical significance. Though there were fewer cases of uterine cancer in the raloxifene group (23/4712) compared with the tamoxifen arm (36/4732), it should be noted that the trial recruited only post-menopausal women more than half of whom had undergone hysterectomy and were also at higher risk for development of breast cancer as determined by the Gail model [92]. There was a slight decrease in the numbers of women suffering from DVT or PE in the raloxifene group, but no difference in incidence of stroke. Though these results of the STAR trial were heralded by some as a breakthrough, they do not show an overwhelming benefit for raloxifene over tamoxifen in terms of efficacy, side-effects and cost.

In theory, the most effective agent for preventing breast cancer should be one which creates an hormonal environment depleted of oestrogens. Aromatase inhibitors are associated with a greater reduction of contralateral breast cancer in adjuvant trials than tamoxifen and are currently under investigation as chemopreventive agents. The IBIS II is a multicentre trial which randomizes healthy women at increased risk of breast cancer to either anastrozole or placebo. Other aromatase inhibitors are likely to be candidates for chemoprevention trials in the future. Though these agents can only be used in post-menopausal women, they could be combined with GnRH agonists as a chemo-preventive strategy in pre-menopausal women. However there are concerns about side-effects of profound oestrogen deprivation (increased fractures, musculoskeletal pain) and it remains unclear for how long women should be treated with a chemo-preventive agent. It is unknown whether a single 'pulse' of treatment (e.g. 5 years) is sufficient and whether any carry-over effect occurs. It would not be feasible to target young teenage girls with a combination of an aromatase inhibitor/GnRH agonist for a prolonged period of time. Delivery of a short pulse of treatment at a critical stage in a woman's life may induce changes in the breast tissue which confer longer term protection and avoids the adverse effects of more prolonged therapy.

Apart from concerns about longer term effects of oestrogen deprivation, there are significant cost issues relating to use of aromatase inhibitors as chemopreventive agents in a managed healthcare system. It has been calculated that the cost of preventing 300 breast cancers with an aromatase inhibitor is between £40 and £50 million pounds compared with £2 million for tamoxifen and £23 million for raloxifene [93]. SERM's can prevent osteoporosis and decrease num-

bers of fractures which potentially incur future additional costs to the health service. The development of a SERM that combines enhanced risk reduction for breast cancer with incidental benefits in other tissues may be a more promising approach to chemoprevention than aromatase inhibitors [94].

CONCLUSIONS

Aromatase inhibitors represent the most significant advance in the endocrine management of breast cancer since the introduction of tamoxifen more than 30 years ago. They now have an established role as first- and second-line treatment for metastatic breast cancer where they offer advantages over tamoxifen and progestins in terms of several clinical parameters including response rates, TTP and side-effect profile. Letrozole is the preferred agent for neo-adjuvant schedules in which it offers slight advantages over other aromatase inhibitors in terms of disease response and progression.

The optimal strategy for incorporation of aromatase inhibitors into standard adjuvant endocrine schedules remains unclear. Benefits in terms of disease-free and overall survival must be balanced against longer term risks (bone health; cognitive function) and costs. There is no clear evidence that initial treatment with tamoxifen for 2 – 3 years prevents subsequent bone loss, but those patients who are not osteopaenic at the start of endocrine treatment are less likely to develop osteoporosis secondary to oestrogen deprivation. An upfront aromatase inhibitor might be indicated in those patients at higher risk of relapse for whom the amplitude of the hazard peak for recurrence is proportionately greater in magnitude and could be suppressed or 'smoothed out' (Epanechnikov kernel) by an aromatase inhibitor more effectively than tamoxifen. As this peak occurs in the first 2 – 3 years after primary treatment, such an effect would only be possible with an upfront aromatase inhibitor and not an early switch [95,96]. For those patients with lower hazards for relapse within the first 2 – 3 years, sequential therapy with tamoxifen (2 – 3 years) followed by an aromatase inhibitor may be more appropriate and cheaper [97]. Finally, it should be noted that a group of older patients may exist with a very low risk of relapse for whom 5 years of tamoxifen remains the most cost-effective adjuvant endocrine option. However, issues of cost are complex and should take account of subsequent adverse events prevented.

Any health economic analysis is dependent on the particular healthcare system within which patients are treated [97,98].

The evidence available at the present time favours an early switch policy for the majority of patients with hormone receptor positive post-menopausal breast cancer. The absolute benefits of an aromatase inhibitor for the average patient are very small in the first 36 months and some argue that the additional benefit of an aromatase inhibitor during the first 2 – 3 years is difficult to justify. Fewer than 5% of patients have an early relapse in the first 2 – 3 years whilst receiving tamoxifen as adjuvant therapy. Punglia and colleagues used a Markov analysis to develop models which simulated 10 year disease-free survival amongst post-menopausal ER positive women with early breast cancer. According to this analysis, switching from tamoxifen to an aro-

matase inhibitor after 2 – 5 years leads to a modest gain in disease-free survival compared with monotherapy with an upfront aromatase inhibitor for 5 years (relative risk reduction 6%). Furthermore, this early switch regimen appeared superior to a late switch from tamoxifen to an aromatase inhibitor after 5 years which did not result in further improvements in 10 year survival [99]. However, Cuzik and colleagues have criticized this analysis on the basis of heterogeneity of endpoints. Some of the trials included used disease-free survival (ATAC, IES, BIG 1-98, ITA) whilst others time to recurrence (MA.17, ABCSG 8, ARNO 95). They maintain that there is a ‘dilutionary effect’ of deaths without recurrence when disease-free survival is used which augments the relative benefits of a switch strategy. A variation of the Markov method was used to demonstrate that when time to recurrence was taken as the primary endpoint, upfront aromatase inhibitors were the favoured option. This so-called ‘deep model’ attempts to explain observed events in terms of underlying biological mechanisms and offers a potential explanation for the greater efficacy of aromatase inhibitors in ER positive/PgR negative tumours compared with ER positive/PgR positive ones [100].

There are concerns about the impact of severe oestrogen depletion in women receiving aromatase inhibitors for chemoprevention. The use of ‘add-on’ agents to minimize the complications of aromatase inhibitors (e.g. biphosphonates) detracts from a preventative strategy in the context of healthy women. Ongoing evaluation of treatment related morbidity will provide important data for accurate analysis of the relative risks, benefits and costs of these agents. This will in turn inform management decisions and permit a more tailored approach to endocrine treatment for individual patient subgroups.

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