

## New Developments in Adjuvant Hormonal Therapy in Early Breast Cancer\*

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### ABSTRACT

For the last 3 decades, tamoxifen has been the cornerstone of endocrine therapy for hormone receptor (HR) positive breast cancers. The selective aromatase inhibitors (AI), such as anastrozole, letrozole and exemestane, are a welcomed addition to the armamentarium for treatment of HR positive breast cancer. Anastrozole is approved as adjuvant treatment in early breast cancer following the publication of the Arimidex, Tamoxifen Alone or in Combination (ATAC) study. It is currently recommended for those at risk for severe tamoxifen-associated side effects or who cannot tolerate tamoxifen. Recent data from the MA.17 study showed that extended adjuvant treatment with letrozole adds benefit to 5 years of tamoxifen. The Intergroup Exemestane Study (IES) and Italian Tamoxifen Arimidex (ITA) Study suggested that switching to AI, such as exemestane or anastrozole, after 2 to 3 years of tamoxifen therapy, is superior compared to continuing with tamoxifen for a total of 5 years in postmenopausal women. Despite these exciting new data, there remain many unanswered questions including the consequences of long term oestrogen deprivation in postmenopausal women, optimal duration of AI treatment and whether it should be given at the start for 5 years or sequenced with tamoxifen after 2 to 3 years or after 5 years of tamoxifen. For the premenopausal women, tamoxifen became standard adjuvant treatment for hormone receptor positive breast cancer barely a decade ago. Of late, the resurgence of interest in ovarian ablation or suppression (through either LHRH agonists, radiotherapy or surgery) may conceivably replace chemotherapy in suitably selected patients. Several studies have shown at least non-inferiority between ovarian ablation or suppression with conventional chemotherapy. Ongoing studies are comparing ovarian ablation or suppression with or without chemotherapy prior to tamoxifen or AI as adjuvant therapy. These studies aim to define the role of chemotherapy in patients who are already receiving ovarian ablation or suppression together with tamoxifen or AI and the added benefit of ovarian ablation or suppression.

*Keywords:* adjuvant, breast cancer, hormonal therapy

### INTRODUCTION

Breast cancer is the most common cancer in females worldwide. In Singapore, the age-standardised rate is 54.9 per 100,000 per year, accounting for almost a quarter of all new cancers diagnosed in Singaporean women.<sup>1</sup>

Breast cancer is a systemic disease. With the exception of the minority with very early stage disease who are cured after surgery alone, the majority of patients require adjuvant treatment to reduce the risk of local recurrence and systemic relapse. Data from the Oxford

Overview by the Early Breast Cancer Trialists' Collaborative Group, a 5-yearly meta-analysis of trials involving breast cancer patients on adjuvant treatment, has conclusively shown benefits in both relapse-free and long-term survival following adjuvant chemotherapy and hormonal treatment with tamoxifen after surgery in suitably selected patients.<sup>2-4</sup>

### TAMOXIFEN — STILL THE GOLD STANDARD?

The use of hormonal therapy for breast cancer dates back to more than a century ago when Beatson observed breast cancers in some premenopausal women regressed after oophorectomy.<sup>5</sup> It was not until about 3 decades ago that tamoxifen was approved for

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use in postmenopausal women with breast cancer primarily due to its relatively low incidence of side-effects. With the availability of data from the Oxford Overview in the late 1980s, tamoxifen became standard adjuvant endocrine therapy in women 50 years or older with hormone receptor (HR) positive breast cancer.<sup>6</sup> Within the last decade, tamoxifen has also been shown to benefit premenopausal women.<sup>2</sup>

Besides anti-tumour efficacy, the widespread use of tamoxifen is accounted for by its tolerability as well as effects on bone loss reduction, favourable lipid profile (higher HDL/LDL ratio) and cardiovascular outcomes.

However, tamoxifen-mediated efficacy is not sustainable. The inevitable efficacy reduction and loss of survival advantage with its extended use arises essentially from its mixed agonist-antagonist properties and the development of endocrine resistance. Tamoxifen's incomplete antagonist activity at the oestrogen receptor (ER) gives rise to venous thromboembolism, uterine bleeding and endometrial cancers.

Although the current recommendation for adjuvant treatment is 5 years of tamoxifen in HR positive breast cancer, it is not uncommon to detect relapses in breast cancer after this period. In an attempt to elucidate the optimal duration of tamoxifen therapy, the National Surgical Adjuvant Breast and Bowel Project B-14 trial randomised 1,152 women (569 placebo; 583 tamoxifen) for an additional 5 years of tamoxifen versus placebo after an initial 5 years of therapy.<sup>7</sup> Through 7 years of follow-up, the disease-free survival (DFS) in the placebo arm was superior (82% vs. 78%,  $P=0.03$ ). The relapse-free survival and overall survival (OS) in the placebo arm were marginally better although not significant (94% vs. 92%,  $P=0.13$  and 94% vs. 91%,  $P=0.07$ , respectively). Extended tamoxifen use was also associated with an increased incidence of cerebrovascular accidents and endometrial cancer. These observations provided a rationale for other agents with demonstrated efficacy in breast cancer to be tested for extended adjuvant therapy in early breast cancer. The selective aromatase inhibitors (AI) have been shown to be at least equivalent and possibly superior in efficacy compared to tamoxifen. While they do not share the side effects of tamoxifen due to its agonistic activity, there is an observed increase risk of skeletal complications arising from osteoporosis. The long-term implications of extreme oestrogen deprivation, particularly on the cardiovascular and neurological systems, are still largely unknown. The emergence of recent data on the benefit of AI in adjuvant therapy raises the question of whether

tamoxifen still remains the "gold standard" of endocrine therapy.

### **SELECTIVE AROMATASE INHIBITORS FOR POSTMENOPAUSAL WOMEN — DO THEY REPLACE TAMOXIFEN?**

The physiological difference between pre- and postmenopausal females in the context of breast cancer lies in the source of oestrogen. Unlike in premenopausal women where oestrogen is mainly ovarian in origin; in postmenopausal females, most of the oestrogen is derived from peripheral conversion of adrenal androgens to oestrogens by the enzyme aromatase present in adipose tissues, muscles and breast tissues. Thus, AI are indicated for use only in postmenopausal women. In the premenopausal women, ovarian suppression is a prerequisite before treatment with an AI.

Since the days when aminoglutethimide was the only AI available for breast cancer treatment, the new generation selective AI are by far more potent, specific and better tolerated. The 3 selective AI — anastrozole, letrozole and exemestane — have been recently reported in several large randomised studies (Arimidex, Tamoxifen Alone or in Combination, MA.17 Study, Intergroup Exemestane Study and Italian Tamoxifen Arimidex study) albeit with different study designs.<sup>8-11</sup> Importantly, all these studies showed improved efficacy and tolerability of AI compared with tamoxifen (Table 1).

### **ATAC TRIAL**

The ATAC trial (Arimidex, Tamoxifen Alone or in Combination) compared anastrozole (Arimidex®), tamoxifen and the combination of both for 5 years as adjuvant endocrine treatment for postmenopausal women. The primary endpoints were DFS, time to the earliest occurrence of local or distant relapse, new primary breast cancer or death from any cause. Secondary endpoints included time to recurrence, distant recurrence and incidence of new contralateral primary breast tumours. There were 9,366 patients recruited from 381 centres (21 countries) between July 1996 and March 2000. Baseline characteristics were well balanced across the 3 treatment groups, including patient demographics, nodal status, tumour size and grade. Approximately 80% of the patient population had HR positive disease. After a median follow-up of 47 months, over 80% completed 3 years of therapy and 46% ( $n=4,310$ ) had been followed up for at least 4 years. The benefit in favour of anastrozole for DFS was significant in patients with HR positive disease (HR

Table 1. Recent randomised adjuvant studies involving aromatase inhibitors.

Trial	Study Arms	Hormone Receptor Positive (HR+) Disease	Patient Accrued	Results (in favour of AI)
ATAC	Anastrozole 5 years Tamoxifen 5 years Both 5 years	84%	9366	4 year DFS 86.9% vs. 84.5% (p=.014) Time to relapse hazard ratio 0.78 (p=.007) Contralateral breast cancer hazard ratio 0.56 (p=.042) Overall survival no difference
MA.17	Tamoxifen 5 years Then placebo 5 years	98%	5187	4 year DFS 93% vs 87% (p=.00008) Contralateral breast cancer 0.5% vs 1% Overall survival improved in node-positive disease
IES	Tamoxifen 5 years Tamoxifen 2-3 years Then exemestane 2-3 years	81.2%	4742	3 year DFS 91.5% vs 86.8% (p≤.001) Contralateral breast cancer 9 vs 20 Overall survival no difference
ITA	Tamoxifen 5 years Tamoxifen 2-3 years Then anastrozole 2-3 years	All ER+, node positive	426	Hazard ratio of relapse 0.36 (p=0.006)
BIG 1-98	Tamoxifen 5 years Letrozole 5 years Tamoxifen 2 years Then letrozole 3 years Letrozole 2 years Then tamoxifen 3 years	NA	8028	DFS hazard ratio 0.81 (in favour of letrozole, p=.003) Overall survival no difference
TEAM	Tamoxifen 5 years Exemestane 5 years	NA	499	NA
NSABP B33	Tamoxifen 5 years Then exemestane 2 years Tamoxifen 5 years Then placebo 2 years	NA	1589	NA

Key: ATAC=Arimidex, Tamoxifen and Combination; IES=Intergroup Exemestane Study; ITA=Italian Tamoxifen Arimidex; BIG=Breast International Group; DFS=Disease-free Survival; NA=Not Available

0.82; 95% CI 0.70–0.96;  $p=0.014$ ). The absolute difference in DFS rates between the anastrozole and tamoxifen arms increased from 1.7% at 3 years to 2.9% at 4 years for the HR positive population. Importantly, the time-to-event curves have continued to diverge with further follow-up. The incidence of contralateral breast cancers remained significantly in favour of anastrozole in the HR positive population ( $n=20$  and  $n=35$  for anastrozole and tamoxifen, respectively) (odds ratio=0.56; 95% CI 0.32–0.98;  $p=0.04$ ). There were fewer contralateral invasive cancers in the anastrozole arm ( $n=17$  versus  $n=31$ ,  $p=0.04$ ). In addition, anastrozole had a more favourable toxicity profile than tamoxifen except for musculoskeletal events and fractures. At a recent update of this study after a median follow-up of 68 months, the observed benefits of anastrozole over tamoxifen persisted.

### MA.17 STUDY

MA.17 is a phase III randomised, double-blind, placebo-controlled trial of letrozole (Femara®) in postmenopausal women with primary breast cancer who had completed 5 years (range 4.5–6) of adjuvant tamoxifen therapy.<sup>9</sup> Patients were randomised to receive either placebo or letrozole (2.5mg, oral) daily for 5 years. Stratification factors included ER status, lymph node status and prior adjuvant chemotherapy. The primary end point was DFS. Secondary end points included OS, safety and quality of life. The sample size in MA.17 was powered to detect a 2.5% difference in 4-year DFS with 80% power at 2-sided 0.05 level. Two interim analyses were scheduled at 171 and 342 events with early termination considered at a nominal significance of  $P=0.00079$ . There were 2,575 and 2,582 women of a median age of 62 years randomised to the letrozole and placebo arms, respectively. The 2 arms were well balanced with respect to performance status, breast-conserving surgery, stage of disease, lymph node status, duration of tamoxifen therapy, previous adjuvant radio- and chemotherapy and HR status. Most of the patients (98%) had HR positive disease. At the first interim analysis after a median follow-up of 2.4 years, 207 events (40% of the events required for final analysis) had occurred. In the placebo arm, 132 events (recurrences and contralateral breast cancer) occurred while 75 occurred in the letrozole arm. The superiority of letrozole over placebo increased with the length of time on letrozole therapy. The DFS at 48 months was superior for letrozole (93% vs. 87%, HR=0.57,  $P=0.00008$ ) which translated into a 43% relative reduction of recurrence risk. There was a trend toward improved overall survival at 4 years for patients on letrozole arm (96% vs. 84%, HR=0.76,  $P=0.25$ ). A

subset analysis of DFS showed that the impact of letrozole in node-positive patients was at least as great as in patients with node-negative disease. At a recent update, there was a significant survival benefit for the subgroup with node-positive disease.<sup>12</sup> Finally, letrozole was fairly well tolerated except for hot flashes (47% vs 41%), arthralgia (21% vs 17%), myalgia (12% vs 10%) and osteoporosis (6% vs 5%).

### INTERGROUP EXEMESTANE STUDY

Another new star in the sky of adjuvant treatment for early breast cancer is exemestane. This recently published double-blind randomised study aimed to test whether after 2 to 3 years of tamoxifen therapy, switching over to exemestane would be more effective than continuing tamoxifen for the remaining 5 years with a primary end point of DFS.<sup>10</sup> Of 4,742 patients enrolled, 2,362 were randomly assigned to switch to exemestane and 2,380 to continue with tamoxifen. After a median follow-up of 30.6 months, 449 events occurred (183 in the exemestane and 266 in the tamoxifen arm). The unadjusted hazard ratio in the exemestane group as compared with the tamoxifen group was 0.68 ( $p<0.001$ ), representing a 32% reduction in risk and an absolute benefit of 4.7% in 3-year DFS. OS was not significantly different, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group. Fewer contralateral breast cancers occurred in the exemestane group (9 vs. 20,  $p=0.04$ ). There were significantly more thromboembolic events and vaginal bleeding in the tamoxifen arm whereas arthralgia and osteoporosis were more prevalent in the exemestane arm.

A very similar but smaller study is the ITA (Italian Tamoxifen Arimidex) trial which randomised patients after 2 to 3 years of tamoxifen to either anastrozole or tamoxifen for a total of 5 years.<sup>11</sup> Similar to the Intergroup Exemestane Study, patients who switched to anastrozole had a better outcome in terms of DFS compared to the tamoxifen arm.

### UNANSWERED QUESTIONS

Although the results of the adjuvant AI studies are consistently positive, there remain several unresolved issues before one can make a universal switch from tamoxifen to AI for patients with HR positive disease. Is it better to give AI as adjuvant treatment at the outset for 5 years, start with tamoxifen and switch afterwards or start AI only after 5 years of tamoxifen? What is the optimal duration of AI therapy? The Breast International Group study (BIG I-98) which has recently completed accrual will hopefully shed light

on these questions. This study compared 5 years of tamoxifen versus 5 years of letrozole versus 2 years of tamoxifen then 3 years of letrozole versus 2 years of letrozole then 3 years of tamoxifen. For now, the long term implications of extreme oestrogen deprivation from AI therapy in postmenopausal women are not clear apart from musculoskeletal events including osteoporosis. The optimal duration of AI, whether it is started at the outset or after switching from tamoxifen or whether for total of 5 or 10 years, is unknown. In the subgroup of patients who have both HR positive and HER2/neu over-expressed disease, studies in metastatic and neoadjuvant settings suggest they might benefit from treatment with an AI rather than tamoxifen.<sup>13-15</sup> This is currently being addressed by the ATAC investigators who are retrospectively analysing the tumour samples of the study patients for HER2/neu over-expression.

Until longer follow-up information from these and other studies are available, it remains for guideline developers, such as American Society of Clinical Oncology and St Gallen's Consensus, to lay down treatment recommendations in this controversial area.<sup>16-17</sup>

#### **OVARIAN FUNCTION SUPPRESSION OR ABLATION FOR PREMENOPAUSAL WOMEN — DOES IT REPLACE CHEMOTHERAPY?**

For premenopausal women with HR positive disease, there is renewed interest in ovarian function suppression which can be achieved either medically with LHRH (luteinising hormone releasing hormone) agonists such as goserelin (Zoladex®), or ablation by surgery or radiotherapy. In suitably selected patients, it may conceivably replace conventional chemotherapy. A study by Love *et al* randomised more than 700 premenopausal women with breast cancer to oophorectomy followed by tamoxifen for 5 years versus observation after primary breast surgery. DFS and OS were superior in patients on the treatment arm with HR positive disease. The limitation of this study was that a tamoxifen-only treatment arm was not part of the trial design. Hence, the added benefit of oophorectomy to tamoxifen could not be elucidated.<sup>18</sup>

Several trials which compared the efficacy of ovarian function suppression or ablation with cytotoxic chemotherapy are shown in Table 2. All except the Austrian study showed equivalence of the 2 treatment modalities. The Austrian Breast Cancer Study Group 05 study reported that the combination of 3 years of goserelin and 5 years of tamoxifen in 1,045 premenopausal women with HR positive disease was

superior to 6 cycles of chemotherapy (intravenous CMF, cyclophosphamide, methotrexate and 5-fluorouracil).<sup>19</sup> However, the chemotherapy used was inferior to classic oral CMF which was the standard regimen.<sup>20,21</sup> The largest of these studies, the ZEBRA (Zoladex in Early Breast Cancer Research Association) trial, randomised more than 1600 pre- or perimenopausal women with node-positive breast cancer to conventional chemotherapy (oral CMF) for 6 cycles versus monthly goserelin (Zoladex®) for 2 years. After a 7-year median follow-up, the DFS and OS of patients with receptor positive disease who underwent ovarian ablation were not inferior to those who had chemotherapy.<sup>22,23</sup> The caveat, however, is that at the time when these trials were initiated, tamoxifen was not yet the standard of care for premenopausal women and hence not included in either treatment arms.

Newer studies which included tamoxifen however, were not designed to address the additional benefit of ovarian function suppression or ablation to 5 years of tamoxifen in women treated with prior chemotherapy. The patients accrued on these studies comprised both pre- and perimenopausal women; the latter would have become amenorrhoeic and probably menopausal at the end of chemotherapy and hence were unlikely to derive additional benefit from ovarian function suppression or ablation versus a subgroup of very young women (below age 40) who would likely remain premenopausal even after chemotherapy.

The ZIPP (Zoladex In Premenopausal Patients) study showed that the combination of ovarian function suppression or ablation and tamoxifen was superior compared to when either treatment was used alone or the observation arm after the completion of adjuvant chemotherapy.<sup>24</sup> However, the duration of tamoxifen treatment was 2 years which is inferior to the standard 5-year recommendation. The Intergroup 0101 study randomised women with node-positive and HR positive disease who have received 6 cycles of CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy to either goserelin for 5 years versus a combination of goserelin and tamoxifen for 5 years versus observation. The combination of chemotherapy followed by goserelin and tamoxifen was associated with a better 9-year DFS. However, the criticism of that study was that a chemotherapy followed by tamoxifen alone arm was not included in the study design.<sup>25</sup> The recent report of the IBCSG (International Breast Cancer Study Group) VIII showed no added benefit from ovarian function suppression or ablation to conventional chemotherapy. However, the subgroup analysis of patients aged 39

Table 2a. Trials comparing ovarian ablation or suppression with chemotherapy.

Trial	Regimen	Patients	N	Results
Scottish	IV CMF×6-8 Oophorectomy	N+	332	No difference
Scandinavian	IV CMF×9 Radiotherapy to ovaries	Stage II HR+	732	No difference
ZEBRA	CMF (PO)×6 Goserelin×2 yr	N+	1640	No difference in ER+ disease
GROCTA 02	CMF (PO)×6 OA+Tam×5yr	N+ HR+	244	No difference
ABCSG 5	IV CMF×6 G×3yr+Tam×5yr	Stage I/II HR+ OS same	1045	Improved relapse free survival in G+T arm
French	FAC×6 OA+Tam	N+ HR+	162	No difference
FASG 06	FEC×6 LHRH+Tam×5yr	N+ HR+	333	No difference

C=cyclophosphamide; M=methotrexate; F=5-fluorouracil; A=Adriamycin; E=epirubicin; G=goserelin; LHRH=luteinising hormone releasing hormone; Tam=tamoxifen; N=number; N+=node-positive; HR+=hormone receptor positive; ER+=estrogen receptor positive; RFS=relapse-free survival; OS=overall survival; ZEBRA=Zoladex in early breast cancer; ABCSG=Austrian Breast Cancer Study Group; FASG=French Adjuvant Study Group.

Table 2b. Trials comparing ovarian suppression/ablation with or without Tamoxifen in those who received chemotherapy.

Trial	Regimen	Patients	N	Results
INT0101	CAF×6 CAF×6, G×5yr CAF×6, G+Tam×5yr	N+ HR+	1503	Improved DFS in Arm 3
IBCSG VIII	CMF (PO)×6 G×3yr CMF×6, G×1.5yr	N-	1060	No difference
ZIPP	'Std chemo' + G×2yr Tam×2yr G+Tam×2yr No further Rx	N+/- HR+/-	2648	Improved RFS & OS with Goserelin

C=cyclophosphamide; M=methotrexate; F=5-fluorouracil; A=Adriamycin; E=epirubicin; G=goserelin; LHRH=luteinising hormone releasing hormone; Tam=tamoxifen; N+=node-positive; HR+=hormone receptor positive; ER+=estrogen receptor positive; RFS=relapse-free survival; OS=overall survival; DFS=disease-free survival; INT=Intergroup; IBCSG=International Breast Cancer Study Group; ZIPP=Zoladex in premenopausal patients.

Table 2c. New ovarian suppression trials in premenopausal women.

Trial	Regimen
SOFT (Suppression of Ovarian Function Trial) - prior chemotherapy allowed	Tamoxifen alone Ovarian Suppression + Tamoxifen Ovarian Suppression + Exemestane
TEXT (Tamoxifen & Exemestane Trial) - concurrent chemotherapy allowed	OS + Tamoxifen OS + Exemestane
PERCHE (Premenopausal Endocrine Responsive Chemotherapy Trial)	OS + CXT → Tamoxifen or Exemestane OS → Tam or Exemestane

OS=ovarian suppression; CXT=chemotherapy

and below might possibly benefit from combination of ovarian ablation and tamoxifen after adjuvant chemotherapy.<sup>26</sup> Notably, in the metastatic disease setting, a recent meta-analysis of studies showed that the addition of ovarian function suppression or ablation to tamoxifen in premenopausal women with breast cancer appeared to be superior to either agent alone.<sup>27</sup>

There are at least 3 large randomised studies — the SOFT (Suppression of Ovarian Function Trial), TEXT (Tamoxifen and Exemestane Trial) and PERCHE (Premenopausal Endocrine Responsive Chemotherapy Trial) which are attempting to define the role of chemotherapy in addition to ovarian ablation and tamoxifen as well as the additional benefit of ovarian ablation to tamoxifen in premenopausal women who have been treated with chemotherapy (Table 2). Until data from these studies are available, “combined oestrogen blockade” after adjuvant chemotherapy is not a standard treatment recommendation for every premenopausal woman with breast cancer.

## CONCLUSION

The recent years have been an exciting era in the treatment of breast cancer not just with the availability of targeted therapies such as monoclonal antibody, trastuzumab (Herceptin®) but also endocrine therapeutic options. For the postmenopausal women, AI are now part of adjuvant options available though the optimal way of prescribing AI and its potential long term toxicities are still uncertain. Ovarian function suppression or ablation for premenopausal women with HR positive breast cancer represents a possible alternative to systemic chemotherapy in a selected group of patients. In addition to research in new agents which are better tolerated and more efficacious than tamoxifen, the main focus of research is now in the area of endocrine resistance and the use of modulating agents, such as farnesyl transferase inhibitors, tyrosine kinase inhibitors or COX-2 inhibitors to overcome this resistance so as to achieve disease control at a higher response rate and of longer duration. The clue to a patient’s treatment outcome and prognosis may ultimately lie in the gene expression profiles of the breast cancer cells which we are only starting to unravel.<sup>28,29</sup>

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