Adjuvant endocrine therapy for postmenopausal women with early stage breast cancer

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While surgery and radiation offer local control of the primary breast tumor, the principal aim of systemic adjuvant therapies is to prevent or delay distant metastases. A large number of randomized clinical trials over the past 20 years have demonstrated the importance of adjuvant endocrine therapy in reducing breast cancer mortality. For postmenopausal hormone receptor-positive patients, tamoxifen has been the standard of care in the adjuvant setting, however, recent developments have led to the introduction of new endocrine agents such as the third-generation aromatase inhibitors. Ongoing studies are evaluating the optimum duration of treatments and the combination and sequencing of different agents to prevent drug-resistance.

Keywords: anastrozole, early breast cancer, endocrine therapy, exemestane, letrozole, postmenopausal, tamoxifen

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Breast cancer epidemiology & risk factors

Breast cancer is a major health problem for women, accounting for approximately 18% of all female cancers and is the leading cause of death among women aged 35–55 years. The risk of developing the disease increases with age, almost half of all cases occur in women aged 50–64 years and a further 30% in women over 70 years of age. Genetic, environmental and endocrine influences contribute to the development of breast cancer [1]. A marked geographical variation for this cancer is evident, highlighting the environmental/lifestyle risk factors. The highest incidences are seen in the Western world and the lowest in Asian and African countries. In the year 2000, an estimated 370,000 deaths worldwide were attributed to breast cancer and over a million new cases were diagnosed [2]. In the UK, since the late 1980s, there has been a sharp decline in the age-adjusted breast cancer mortality rates (30% in a 10–12 year period). Undoubtedly a major factor for this decline has been the widespread introduction of adjuvant endocrine interventions, specifically tamoxifen [3]. This review outlines the current status and future of adjuvant endocrine therapy options for postmenopausal women with early stage hormone-responsive breast cancer.

Adjuvant endocrine therapy: past, present & future

It has long been established that lifetime exposure to sex hormones, particularly estrogen and its metabolites, has a pivotal role in the etiology of breast cancer, influencing both risk of the disease and growth of pre-existing tumors [4]. It is over 100 years since the discovery that bilateral oophorectomy in premenopausal women with locally advanced disease resulted in tumor regression [5].

Central to the major advances in endocrine therapy has been the identification of the estrogen receptor (ER) as the pivotal protein controlling estrogen action. Approximately two-thirds of all breast tumors are ER-positive [6]. In postmenopausal women there are two main strategies for counteracting the stimulatory growth effects of estrogen on breast tissue. The first is to antagonize the binding of estrogen to its receptor (e.g. with an antiestrogen) and the second is estrogen deprivation (using an aromatase inhibitor) [7–9].

Tamoxifen monotherapy was the first hormonal intervention to demonstrate efficacy in the adjuvant context [10–12]. In 2003, the 8th International Consensus Conference on adjuvant therapy of primary breast cancer in St Gallen, Switzerland, updated its recommendations for endocrine treatments outside of clinical trials [13]. For postmenopausal women with early stage breast cancer, tamoxifen remains the recommended therapy unless there is a contraindication to the drug, for instance, a history of thromboembolic disease. In that case, the third-generation aromatase inhibitor, anastrozole (Arimidex®, AstraZeneca) should then replace tamoxifen [14]. For enhanced efficacy, it is now recommended that initiation of tamoxifen should be postponed until after completion of chemotherapy. A recent intergroup trial (INT-0100) supported previous pre-clinical data showing

that tamoxifen inhibited the effectiveness of certain chemotherapy agents when administered concurrently [15]. Interim results from the GEICAM 9401 study have shown a similar trend. Findings between both trials suggest that the sequential addition of tamoxifen to a chemotherapy regimen is favorable to concurrent use [16].

Ongoing clinical trials are exploring the long-term risks and benefits of more recent alternatives. With their demonstrated superiority over tamoxifen in the treatment of advanced breast cancer, the third-generation aromatase inhibitors are currently challenging tamoxifen as a first-line adjuvant treatment option for early breast cancer. Data from recent studies have also provided valuable information on the sequencing of hormonal manipulations.

Future prospects include ER down-regulators, such as fulvestrant (Faslodex®, AstraZeneca), as novel options in the sequencing and combining of treatments. Prognostic biomarkers such as the ER and the human epidermal growth factor receptor 2 (HER-2) already provide valuable information regarding outcome and are important considerations in treatment decisions. It is therefore envisaged that ongoing genomic and proteomic studies will identify new biomarkers for breast cancer prevention and treatment, enabling the most effective treatment regimens to be tailored to individual patient profiles [17].

Antiestrogen therapy

Selective ER modulators (SERMs) compete with endogenous estrogen for binding to the receptor and act as ER agonists in some tissues while acting as ER antagonists in others [18–20]. Important estrogen-sensitive tissues in postmenopausal women include breast, endometrium, bone, liver and CNS. Many SERM compounds have been identified with differing agonist/antagonist profiles in these different tissues. The 'ideal' SERM would have estrogen agonist effects on the brain, bone metabolism and the cardiovascular system, neutral effects on the uterus and estrogen antagonist effects on breast tissue. Unfortunately none have matched these exact criteria to date. Tamoxifen, raloxifene (Evista®, Lilly) and toremifene (Fareston®, Orion Pharmaceuticals) are the SERMs used in current clinical practice. Tamoxifen and toremifene are approved to treat breast cancer and raloxifene for the treatment of osteoporosis. Although newer compounds have been under development (idoxifene, droloxifene, ospemifene, lasofoxifene, arzoifene and MDL 103,323) none have demonstrated superior efficacy over tamoxifen.

Tamoxifen

The 1995 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of 55 trials involving 37,000 women with breast cancer concluded that 5 years of tamoxifen results in an up to 47% (in ER-positive disease) relative reduction in recurrence risk and that the proportional reduction in mortality is 26% at the same time interval [6]. In addition, the annual incidence of contralateral disease is approximately halved. This substantial level of benefit has been confirmed in the widely presented, but as yet still unpublished, 2000 EBCTCG overview. Due to its agonist properties however, long-term use is associated with an increased risk of endometrial cancer with longer exposure resulting in larger risk. The incidence of thromboembolic events is also increased. Retinopathy has been reported in women given high doses of tamoxifen [21], however, ocular toxicity is rare in the current clinical setting of long-term, low-dose tamoxifen use [22]. Tamoxifen has a consistently reported beneficial effect on lipid profiles, reducing low-density lipoprotein (LDL) cholesterol by about 20%. This however has not been associated with the expected corresponding reduction in coronary heart disease deaths, although reductions in nonfatal myocardial infarctions have been reported. An incidental clinical benefit afforded by its estrogenic effect is its protective effect against osteoporosis [23–25]. Common non life-threatening but significant side effects include vasomotor symptoms, gastrointestinal disturbance, atrophic vaginitis and changes in sexual functioning [26].

It would appear that 5 years of adjuvant tamoxifen therapy is more effective than shorter durations [6,27]. Early results from trials designed to investigate optimum duration beyond 5 years have been controversial [28–31]. The National Surgical Adjuvant Breast and Bowel Project (NSABP)-B14 trial reported that relapse-free survival was worse in patients treated for 10 years than those treated for 5 [29], whereas a Scottish trial reported no significant difference in recurrence when treatment was extended [28]. Both of these studies randomized patients with no axillary lymph node involvement. In contrast, a small Eastern Cooperative Oncology Group (ECOG) trial, with a lymph node-positive patient population, demonstrated an advantage for 10 years of tamoxifen therapy [30,32]. These

such as fadrozole and formestane, although more specific and less toxic, failed to demonstrate superior efficacy over conventional drugs in the second-line or first-line setting [61–63].

The third-generation orally active aromatase inhibitors anastrozole, letrozole (Femara®, Novartis), and aromatase inactivator exemestane (Aromasin®, Pfizer) were introduced in the late 1990s and represent a significantly more potent, specific and better tolerated class of drugs [64,65]. These agents can be divided into two groups according to their structure and mechanism of action. Anastrozole and letrozole are nonsteroidal inhibitors which bind reversibly to the aromatase enzyme (Type II inhibitors). Contrastingly, exemestane is a steroidal inactivator binding irreversibly and competing with the natural ligand (Type I inhibitor). The greater estrogen suppression afforded by these third-generation compounds correlates with their improved clinical efficacy [66–68]. Presently the third-generation aromatase inhibitors and inactivators represent the greatest hope for improving the effectiveness of current adjuvant endocrine therapy.

Four international randomized Phase III trials have compared their effectiveness against megestrol acetate (Megace®, Bristol–Myers Squibb) as second-line therapy following tamoxifen failure in advanced disease [67,69,70]. Each trial demonstrated their clinical superiority and enhanced safety profile. Consequently, they are now established as the agents of choice in this setting, relegating megestrol acetate to third- or fourth-line use.

Following on from this, results of randomized Phase III studies evaluating their effectiveness against tamoxifen as a first-line treatment option for advanced disease have now been published. Two studies enrolling a combined total of 1021 patients, compared anastrozole with tamoxifen and one compared letrozole with tamoxifen in 907 patients [64,65,71]. The letrozole study protocoled a cross-over to the alternate treatment arm at progression or discontinuation due to adverse events. This trial was therefore a more complete test of hormone therapy sequencing. The trial reported that letrozole was superior with respect to the key variables of overall response rate and time-to-progression [65]. Although an updated analysis failed to show a statistically significant difference in median overall survival, survival was improved in the letrozole arm over the initial 2 years of treatment [72]. The two anastrozole studies, the North American and the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) trials were designed similarly and were prospectively intended for combined analysis [73]. Results demonstrated a trend for superiority with anastrozole, but only in the subgroup of ER-positive tumors did the difference reach statistical significance in the combined analysis.

Comparisons between these three studies were made difficult due to the differences in the trial population. In particular, the percentage receiving prior adjuvant endocrine therapy was about 10% for the European TARGET study [64] and about

Table 1. Identification of the most meaningful patient population from some of the recent adjuvant aromatase inhibitor trials.

Study population	Design	Hazard ratio (HR) for disease-free survival (DFS)	Confidence interval (CI)	Number of patients (approx.)	Refs.
ATAC ER^{+ve} subset	Anastrozole vs Tamoxifen	0.78 (p = 005)	0.69–0.93	5200	[77]
ITA ER^{+ve}, lymph $node^{+ve}$	Anastrozole vs Tamoxifen (after 2 years tamoxifen)	0.36 (p = 0.006)	0.17–0.75	426	[80]
IES ER^{+ve} subset	Exemestane vs Tamoxifen (after 2–3 years tamoxifen)	0.64 (p-value not stated)	0.52–0.79	3853	[78]
(NCIC)MA17 (2% ER-unknown)	Letrozole vs Placebo (after 5–6 years tamoxifen)	0.58 (p = 0.00008)	0.43–0.75	5187	[81]

Estrogen receptor-positive subsets have been extracted from ATAC and IES. The whole study population of the ITA study was ER/lymph node-positive and only 2% of the patient population of MA17 were ER-unknown, indicating probable contamination by ER-negative tumors of less than 1%. ATAC: Arimidex, Tamoxifen, Alone or in Combination study; ER: Estrogen receptor; ITA: Italian Tamoxifen: Anastrozole study; IES: International Exemestane Study; (NCIC) MA17: National Cancer Institute of Canada MA17 study.

20% for the other two. Additionally, the percentage of patients with hormone receptor-unknown tumors varied considerably, between 1 and 55%. A key difference with the letrozole study however was the very careful method of analysis with respect to subgroups, separating out the effect on ER/progesterone receptor (PgR)-positive tumors and the putative impact of prior adjuvant endocrine therapy. An open-label European Organization for Research and Treatment of Cancer (EORTC 10951) Phase III trial compared exemestane with tamoxifen as first-line therapy in postmenopausal women with advanced disease; progression-free survival being the primary endpoint [74]. Although analysis using the log–rank test failed to demonstrate a statistically significant progression-free survival advantage for exemestane, the Wilcoxon sensitivity test analysis was positive in favor of exemestane. Updated results presented at the 40th annual meeting of the American Society of Clinical Oncology (ASCO, 2004, LA, USA) showed progression-free survival to be significantly longer under exemestane ($p = 0.028$), with a hazard ratio (HR) of 0.84 (95% confidence interval (CI), 0.67–1.05) in favor of exemestane.

Numerous ongoing clinical trials are now comparing the efficacy and tolerability of these third-generation aromatase inhibitors with tamoxifen as adjuvant therapy for postmenopausal women with early stage breast cancer (**Figure 2**) [75]. Pertinent results from some of the recent studies to have reported are outlined in **Table 1**. Associated substudies are collecting valuable data on the effects of these agents on quality of life, menopausal symptoms, end-organ functions such as bone mineral density, serum lipid levels and cognitive function.

The first major report of an adjuvant study evaluating anastrozole in this setting came from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [76]. This 9366 patient study compared anastrozole alone or in combination with tamoxifen, relative to tamoxifen alone as a 5-year adjuvant treatment for postmenopausal women with early breast cancer. There are currently too few deaths to allow meaningful analyses of overall survival. However initial results with a median follow-up of 33.3 months showed that anastrozole is significantly superior to tamoxifen with regards to relapse-free survival and incidence of contralateral disease [76]. Combination treatment was equivalent to tamoxifen and significantly worse than anastrozole alone, resulting in the discontinuation of this arm.

In terms of tolerability, anastrozole was significantly better than tamoxifen with respect to endometrial cancer ($p = 0.02$), vaginal bleeding and discharge ($p < 0.0001$ for both), cerebrovascular events ($p = 0.0006$), venous thromboembolic events ($p = 0.0006$) and hot flushes ($p < 0.0001$). Tamoxifen however was associated with significantly less musculoskeletal disorders and fractures ($p < 0.0001$). Data updated at 47 months continued to favor anastrozole over tamoxifen [77]. In the ER-positive population anastrozole improved disease-free survival with a HR of 0.82 (95% CI, 0.71–0.96; $p = 0.014$). In terms of actual benefit however, the disease-free survival translates to a modest absolute improvement of 2.9% (89 versus 86.1%). Further follow-up is required and ongoing to determine long-term outcomes and further define the benefit–risk of anastrozole as an adjuvant therapy option. Despite this however, these early positive results have led to the approval of anastrozole in the USA for use as an adjuvant hormonal therapy for postmenopausal women with hormone receptor-positive breast cancer, and in the UK for some groups of patients who have relative/absolute contraindications to tamoxifen use.

The Tamoxifen and Exemestane Adjuvant Multicentre (TEAM) trial is a large international randomized phase III study originally designed to investigate the efficacy and long-term tolerability of 5 years adjuvant exemestane versus 5 years adjuvant tamoxifen in postmenopausal women with early stage breast cancer. However following publication of interim results from the International Exemestane Study (IES) [78] the TEAM trial design has been revised. The new question will therefore ask whether a sequential strategy of tamoxifen followed by exemestane is better than exemestane monotherapy. The experimental arm will remain 5 years of exemestane therapy and the original control arm of 5 years of tamoxifen will be replaced – patients randomized to tamoxifen will now cross-over to exemestane after 30–36 months of tamoxifen. The TEAM study also presents an opportunity for the prospective collection of tumor samples, which will allow the examination of potential predictive markers of response/nonresponse to therapy, such as the over-expression of the HER family and downstream targets.

In an attempt to counteract tamoxifen resistance, several studies are challenging the concept of adjuvant tamoxifen monotherapy. One of the first trials to indicate that aromatase inhibitors

was reported (4.1 vs. 3.6% for letrozole and placebo respectively; p = 0.40). Although more diagnoses of new-onset osteoporosis were evident in the letrozole group (5.8 vs. 4.5%; p = 0.07), the clinical fracture rate between the two groups did not reach statistical significance (3.6% with letrozole versus 2.9% with placebo; p = 0.24). Due to the early discontinuation the effects of letrozole on bone metabolism may have been underestimated. As a precaution therefore it was recommended that patients receiving long-term letrozole should take calcium and vitamin D as an aid for the prevention of osteoporosis. Ongoing monitoring of toxicity for patients receiving letrozole is planned. Although long-term toxicity differences will be obscured by cross-over, other ongoing studies will contribute valuable information regarding adverse events. Due to the unavoidable but subsequently controversial early closure the optimal duration of treatment will remain undefined. In an update to the initial findings however, a pre-planned analysis, presented at the 40th annual ASCO meeting, 2004 (LA, USA), has now revealed a survival advantage in the node-positive population; letrozole was reported to have reduced mortality by 39% (p = 0.04) in this patient subset. This makes it the first study to demonstrate a survival advantage for an aromatase inhibitor in the adjuvant setting.

Closure of this trial and the subsequent related closure of the NSABP-B33 exemestane trial, a study with a similar design to MA-17 addressed to answer a similar question with exemestane replacing letrozole, has generated much discussion with respect to the appropriate definition of early stopping rules and the potential negative impact of data release ahead of full maturity [82–84]. There is no solution to this scientific and ethical dilemma, although a compromize proposal where future trials will report distant relapse-free survival may to some extent resolve the difficulties created as a result of data released from publication of recent trials [84].

The MA-27 trial is a head-to-head comparison of two aromatase inhibitors, anastrozole and exemestane, as adjuvant therapy. This study also includes the addition of the cyclooxygenase (COX)-2 inhibitor, celecoxib. The COX-2 pathway is an inducible and up-regulated pathway in both invasive and pre-invasive cancers; COX-2 over-expression being associated with angiogenesis, cell growth/invasion, inhibition of apoptosis, tumor-associated inflammation and association with HER-2 upregulation and aromatase induction [85]. Celecoxib (Celebrex®, Pfizer) is an approved chemoprevention agent for familial polyposis of the colon and preliminary data suggest a synergistic effect between celecoxib and exemestane [86–88]. The Randomized European Celecoxib Trial (REACT) is an International Collaborative Cancer Group/Breast International Group (ICCG/BIG) phase III study currently enrolling both ER-negative and ER-positive primary breast cancer patients to celecoxib or placebo following chemotherapy, with exemestane as the chosen hormonal therapy for the hormone receptor-positive subgroup. In addition this study will explore the role of COX-2 inhibition in conjunction with exemestane in patients receiving chemotherapy and will explore the role of COX-2 in the hormone receptor-negative population.

An important consideration for adjuvant therapies in early breast cancer, where drugs will be administered for long periods of time, is the side-effect profile. The preliminary results presented for ATAC, MA-17 and the IES, although impressive, are still too immature to allow a complete risk: benefit assessment of aromatase inhibitors in the adjuvant setting. In the short-term aromatase inhibitors on the whole appear better tolerated, with a low incidence of serious adverse events reported [76,78,81]. However musculoskeletal disorders appear to be more prevalent with aromatase inhibitor use. With regards to long-term consequences, unlike tamoxifen, aromatase inhibitors are not associated with increased endometrial cancers or venous thromboembolism [76]. Limited data are available on cardiovascular and cognitive effects. Based on the mechanism of action and preliminary results from the three large adjuvant trials reported to date increased bone demineralization is likely to be a significant issue [76,78,81]. The extent to which this can be compensated for with supportive medications such as calcium, vitamin D or bisphosphonates remains to be determined. However, it is encouraging to note that preliminary data from an Austrian study has shown that the bisphosphonte zoledronic acid (Zometa®, Novartis Pharma) can significantly reduce bone mineral density loss associated with adjuvant ovarian suppression combined with anastrozole [89].

Endocrine therapy for breast cancer has come a long way from invasive surgical procedures to the use of potent and highly specific oral compounds. Tamoxifen has had, and continues to have, a significant role in the management of

the disease however, the development of third-generation aromatase inhibitors provides a wider range of choices in hormonal manipulation. These agents selectively reduce peripheral estrogen biosynthesis and provide a well-tolerated targeted therapy option for hormone-dependent breast cancer. Aromatase inhibitors are producing higher response rates and longer duration of response in advanced disease. The development of 'pure' antiestrogens offers an additional dimension to the optimal sequencing of agents. Focus is now being directed towards searching for surrogate markers in the neoadjuvant setting that can predict the responsiveness and prognosis with adjuvant therapy. As part of a prospective substudy analysis, a recent neoadjuvant randomized Phase III trial has reported that letrozole was more effective than tamoxifen for HER-1 and/or HER-2 positive, ER-positive primary breast cancers; differences in response rates between the two treatments being more marked for the above tumor characteristics (88 vs. 21%; p = 0.0004) [90]. This emphasises the importance of predictive biomarker analysis and it is now widely recognized that alongside new clinical trials, associated translational science protocols must be built into the trial design.

Expert opinion

Worldwide well over one million postmenopausal women are currently taking tamoxifen and thousands of deaths are being prevented every year. Adjuvant tamoxifen therapy for early breast cancer has probably had the largest impact on cancer outcome of any systemic anti-cancer therapy in terms of reduced global mortality. Tamoxifen will undoubtedly take some beating but the efficacy of tamoxifen is clearly inferior to anastrozole as first-line therapy in the initial few years after treatment for early breast cancer and there is little to suggest that this difference will not continue to increase over a standard 5 year course of endocrine therapy.

Exemestane has also been demonstrated to outperform tamoxifen in the second part of a 5 year course of endocrine therapy; with confirmatory data suggesting the same is probably also true for anastrozole. Letrozole comparisons with tamoxifen are awaited but here too an impressive performance after 5 years of tamoxifen suggests a potential role, however concerns over the absence of a continued tamoxifen arm in the MA17 study will remain until data from the ATLAS and ATTOM studies define the role of prolonged tamoxifen.

What is the price of this increased efficacy? Fear of the unknown is clearly having a profound effect on current guidelines and licensing decisions. We have learned to live with the downside of tamoxifen for so long that we have become comfortable handling the gynecological side effects, including endometrial cancer. The increased risk of thrombosis is accepted because, until recently, there have not been any alternatives. When faced with osteoporosis however there appears to be a huge reluctance to accept the burden of responsibility for the majority of our patients yet there is little reluctance to turn to adjuvant aromatase inhibitors in patients with contraindications to tamoxifen, with widespread variation in the degree of osteovigilance adopted in these patients. There is currently little hard data to work with, but with effective treatment and preventative therapies available to manage osteoporosis, the probability is that osteoporotic problems can be addressed. Clinical trials are currently recruiting that will help define appropriate management strategies for dealing with aromatase inhibitor-induced osteoporosis. The increased healthcare burden of this will to a greater or lesser extent be offset by reduced gynecological intervention.

The financial burden of widespread adoption of aromatase inhibitor use in the adjuvant context is of course at one level very clear, with aromatase inhibitors currently about 10 times more expensive than tamoxifen. Tentative exploration of health economics however places aromatase inhibitors firmly in the realms of cost-effective interventions [91]. The issue of whether this is an affordable option is as much a political discussion as it is a health economic science. There is undoubtedly a need to protect patients from the overenthusiastic early adoption of new therapies. The arrival of mature data with survival endpoints is going to be needed before the most sceptical are convinced that aromatase inhibitors should be made available to all patients. The current environment of research ethics is making the delivery of this data increasingly difficult as researchers are required to respond to each twist of the data thus distorting the ability to produce answers to the questions posed several years earlier.

Aromatase inhibitor therapy will with little doubt, become part of everyday practice at some future point in time. The optimization of where aromatase inhibitor therapy fits into the overall endocrine package however needs

Highlights

- Tamoxifen has a long-established pedigree for reducing breast cancer recurrence and death in postmenopausal women with early stage breast cancer.
- The third-generation aromatase inhibitor anastrozole (Arimidex®, AstraZeneca) shows superior efficacy to tamoxifen in preventing early relapses in estrogen receptor(ER)-positive postmenopausal women with early stage breast cancer.
- Exemestane (Aromasin®, Pfizer) is superior to continued tamoxifen after 2–3 years prior tamoxifen therapy.
- Letrozole (Femara®, Novartis) is superior to placebo after completion of 5 years tamoxifen treatment.
- Long-term follow-up is not available for any third-generation aromatase inhibitor study.
- The optimal sequencing of multiple endocrine agents has not been defined.

further definition. The introduction of aromatase inhibitors after either short duration (2–3 years) or possibly long-term (5 years) tamoxifen provides benefit and with an impressive reduction in risk of relapse, but this approach inevitably condemns a small proportion of women to an early relapse that would have been prevented by immediate use of an aromatase inhibitor. It remains to be determined if this early attrition can be recovered by a sequential strategy. The sequential use of tamoxifen or other SERM after aromatase inhibitor therapy is a potential method of introducing a sequential regimen using different endocrine agents and uses the most active agent first but is associated with theoretical concerns over the sensitization of breast cancer cells to the agonist effects of a partial agonist with potentially detrimental consequences. The detailed analysis of the BIG-FEMTA trial involving an arm with just such a sequence is therefore of great interest. The unravelling of the optimal sequence and timing of different endocrine therapies will only be resolved by the study of very long-term outcomes from randomized comparisons of different strategies. The current cohort of ongoing studies will not fully address all of the unknown parameters and the issue of duration combined with sequence will need evaluation.

Outlook

The notion however that a unified optimal sequence and duration that is applicable to all patients is probably a fallacy and that underlying the overall effects of different treatments lie individual patients with unique but potentially classifiable tumors with diverse characteristics that may need dissimilar management strategies. Characterization and individualization of therapies based on gene and proteomic expression profiling is a massive research undertaking but could direct us towards a simple set of key gene expression and/or protein expression profiles to guide hormonal, chemotherapeutic and new biological agent adjuvant strategies that will define optimal treatment packages for women with early breast cancer. Within the next 5 years the clinical reservations regarding adjuvant aromatase inhibitors and the financial obstacles to access aromatase inhibitors are likely to be overcome. Therefore, unless we are able to identify a cohort of women who will gain no additional benefit or who will have a better outcome with tamoxifen, most postmenopausal women will be treated with aromatase inhibitor monotherapy or a sequential combination utilizing an aromatase inhibitor. Which aromatase inhibitor will we use? We may see the first results of comparative trials using competitor aromatase inhibitors that could profoundly affect our choice of inhibitor, but in the meantime we will need to make choices based on the strength of the evidence in each patient's individual circumstances in relation to efficacy and side effect profile. A critical issue will be to determine if differences in bone toxicity exist between the different aromatase inhibitors.

Information resources

The publishers of major oncology and specialist breast cancer journals provide easily accessed online websites, enabling access to abstracts and in certain cases to full text articles.

Recommended bookmarks include:

- Journal of Clinical Oncology
  www.jco.org
- American Society of Clinical Oncology
  www.asco.org
- The New England Journal of Medicine
  www.nejm.org
- British Medical Journal
  www.bmj.com
- European Journal of Cancer
  www.cancerres.aacrjournals.org

Pharmaceutical company websites also provide a useful resource to new therapeutic developments and ongoing research:

- www.pfizer.com
- www.astrazeneca.com
- www.novartis.com

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