Endocrine therapy in locally recurrent and metastatic breast cancer

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Introduction

Metastatic breast cancer is considered incurable, and so the goal of treatment is to prolong survival and optimise palliative care. Although the treatment of metastatic breast cancer may include surgery and radiation therapy, management of the disease is generally focused on systemic therapies. The guidelines for systemic therapy are also applicable in locally recurrent disease not amenable to local treatment modalities.

Endocrine therapy for advanced breast cancer was introduced more than 100 years when Beatson demonstrated that oophorectomy could result in regression of skin metastases in a woman with breast cancer. Subsequent research focused on other methods of endocrine ablation. Both adrenalectomy and hypophysectomy proved to be effective palliative approaches, but with substantial morbidity and mortality.

Approximately 60 years ago oestrogens, androgens and gestagens became available and demonstrated activity similar to ablative procedures.

The first-generation aromatase inhibitor aminoglutethimide was introduced in the 1960s, and the first SERM (selective oestrogen receptor modulator) tamoxifen, in the early 1970s. Since then, other SERMs (toremifene, droloxifene, idoxifene, fulvestrant), the second-generation aromatase inhibitors (formestane, fadrozole) and the luteinising hormone-releasing hormone (LHRH) analogues (buserelin, goserelin) have been introduced and, lastly, during the 1990s the third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) entered clinical trials.

Classes of endocrine therapy and mode of action

Although the mechanism of action differs, the ultimate aim of the different endocrine therapies is to inhibit the oestrogen-dependent growth of the tumour cell.

The mode of action of the ablative therapies (oophorectomy, hypophysectomy, adrenalectomy) is via removal of the organ synthesising oestrogens or precursors of oestrogens.

The action of the SERMs is via interference with the oestrogen receptor-mediated transcription. There are 2 classes of SERMs, the non-steroidal and the steroidal. The non-steroidal SERMs include tamoxifen, toremifene, droloxifene and raloxifene. A steroidal SERM in clinical use is fulvestrant, which is a structural derivative of oestradiol with a long hydrophobic side chain at the 7-α position.

The two types of anti-oestrogen, steroidal and non-steroidal, appear to have different mechanisms of action, which may account for differences in their activity and side-effect profiles. The triphenylethylene anti-oestrogens (tamoxifen, toremifene and droloxifene) bind to the oestrogen binding sites of oestrogen receptor (ER) monomers, which then combine to form dimers. This process of dimerisation facilitates binding of the ER to specific oestrogen response elements (ERE) in the vicinity of oestrogen-regulated genes. The ER protein contains two trans-activating functions (TAFs), both of which are activated when oestrogen binds to the ERE, resulting in gene transcription and gene repression associated with the effect of oestrogen. Tamoxifen binding to the ER results in activation of TAF1 in a manner similar to oestrogen, but activation of TAF2 is compromised by tamoxifen. Thus, tamoxifen is a partial agonist because it activates TAF1 and an antagonist because it inhibits TAF2 [1].

The more recently developed non-steroidal anti-oestrogens (toremifene, droloxifene, raloxifene, idoxifene) generally, in the immature rat uterus model, have less agonistic and more antagonistic action than tamoxifen [1].

The activity of the steroidal anti-oestrogens appears to be different. Fulvestrant binds to ER, but because of the long chain on the 7-α position of the molecule, it appears to sterically hinder receptor dimerisation. There is evidence that ER degradation is

increased with an associated reduction of detectable ER molecules in the cell. In the absence of receptor dimerisation, binding of ER to EREs may be abolished or attenuated. *In vitro*, virtually no transcriptional activity of ER has been detected in cells treated with pure anti-oestrogens [1].

Some may argue that fulvestrant is not a true SERM because it lacks selective agonist/antagonist effects in different tissues and acts through a fundamentally different mechanism of action. Others have suggested that the drug represents one end (i.e. pure anti-oestrogen) of the SERM spectrum, with oestrogen as a pure agonist at the other end, and all other SERMs falling somewhere in between.

The mode of action of the inhibitive therapies (LHRH analogues, aromatase inhibitors) is via inhibition of the enzymes involved in the synthesis of oestrogens. The LHRH analogues inhibit the synthesis of LH and follicle-stimulating hormone (FSH) leading to secondary suppression of the oestrogens synthesised in the ovary. The action of the aromatase inhibitors is via inhibition of the enzyme aromatase, responsible for the conversion of androgens to oestrogens. In postmenopausal women, the source of oestrogens is the androgens produced in the adrenals and converted to oestrogen in the peripheral tissue, especially fat tissue. In premenopausal women, the major source of oestrogen is from ovarian secretion following the conversion from androgen.

Two types of aromatase inhibitors exist — the steroidal type I inactivators (formestane, exemestane), and the non-steroidal type II inhibitors (aminoglutethimide, fadrozole, anastrozole, letrozole). The steroidal inactivators compete with the endogenous substrates, androstenedione and testosterone, for the active site of the enzymes, where they act as false substrates. They are processed to intermediates that bind irreversibly to the active site, causing irreversible enzyme inhibition. *De novo* synthesis of aromatase is required to regain enzymatic activity [2]. The non-steroidal inhibitors also compete with the endogenous substrate for access to the active site, thereby competitively preventing androgens from binding by forming a coordinate bond to the haeme iron atom [2]. Whereas the first-generation aromatase inhibitor aminoglutethimide caused incomplete suppression of circulating oestrogens and was non-selective in the inhibition also of the synthesis of mineralo- and glucocorticoids, the third-generation inhibitors (exemestane, anastrozole and letrozole) are highly selective in the inhibition of the aromatase enzyme and highly effective, causing a nearly complete suppression of *in vivo* enzymatic activity [2]. One randomised clinical study compared anastrozole in the suppression of circulating oestrogens and the inhibition of whole body aromatisation with anastrozole and letrozole. For both endpoints, letrozole documented superior efficacy [3]. The mechanism of action of the additive therapies (androgen, oestrogen, gestagens) is poorly elucidated, but seems to comprise effects as well on the oestrogen receptor as on the hypophyseal feedback mechanism.

There has been an increasing understanding of the function of ER, including its interaction with co-activators and suppressors, the existence and relevance of the extra-nuclear receptor and the "cross-talk" between the ER and growth factor signalling pathways. This may also help to better understand the development of endocrine resistance to a specific endocrine therapy, but also the lack of complete cross-resistance between different endocrine agents.

Selection of patients for endocrine therapy

The treatment selection for an individual patient with advanced breast cancer is usually based on certain clinical and paraclinical criteria. Factors that would reliably predict response to a particular treatment or class of agents would therefore be of benefit to both clinicians and patients. The best predictor of response to endocrine therapy is the expression of the oestrogen and progesterone receptor (ER and PgR) in the tumour tissue. Generally, staining of 10% or more of the cells by immunohistochemical methods is used to select patients for endocrine therapy although this is still a controversial area of research. There is a growing interest in the recognition and validation of other factors. Although progress is being made, much controversy still exists. For example, the overexpression of the HER-2 receptor protein in breast cancer defines a group of patients likely to benefit from treatment with the monoclonal antibody trastuzumab. Some trials suggest that the overexpression of HER-2 or Topo II in breast cancer may predict the response to anthracycline-based chemotherapy. Less certain are the claims that HER-2 overexpression predicts for reduced sensitivity to cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy or tamoxifen. Other possible predictive factors include P53 mutations in determining resistance to chemotherapy and hormonal therapy, and low thymidylate synthetase tumour levels as a marker for sensitivity to therapy with fluoropyrimidines. Further advances in this area of research hold the promise of better therapy individualisation for patients with advanced breast cancer.

So far, it is generally agreed that the treatment of choice is endocrine therapy if the tumour expresses

ER/PgR receptors, whereas chemotherapy is reserved for patients with receptor-negative tumours or for patients who are non-responsive to endocrine therapy. An exception from these general guidelines is the recommendation to use chemotherapy in patients with extensive symptomatic visceral involvement of the disease, irrespective of receptor status. As response to first-line endocrine therapy predicts response to subsequent other types of endocrine therapy, patients who achieve clinical benefit (i.e. who achieve a complete a partial response or no change for at least 6 months) from first-line endocrine treatment are routinely offered a second-line endocrine therapy. Clinical benefit as an endpoint in endocrine therapy of advanced breast cancer has been introduced following the demonstration that time to progression and duration of survival is similar in patients who achieve a response and no change lasting at least 6 months.

Combined cytotoxic–endocrine therapy

Clinical research has sought to determine if a combination of chemotherapy and endocrine therapy is more effective than either therapy alone. Theoretically, the combination may have several advantages. Since endocrine therapy is generally well tolerated by the patients, it combines easily with chemotherapy. Furthermore, since chemotherapy and hormonal therapies have different mechanisms of action, the effect might be at least additive.

The available data from randomised trials of chemotherapy vs. chemotherapy plus endocrine therapy (ablative, additive or competitive) have previously been extensively reviewed [4]. Although the biological rationale for the combined therapy appears sound in theory, an additive effect has been demonstrated in only some clinical trials. In this respect, combination of cytotoxic therapy with either oophorectomy or tamoxifen has been best elucidated. In these studies, an increase in response rate to what would be expected on the assumption that the two treatment modalities have independent biological actions has been observed. However, only a minority of the studies have demonstrated combined chemo-endocrine therapy to be superior to chemotherapy alone with respect to duration of survival.

The Australian and New Zealand Breast Cancer Trial randomised postmenopausal patients to first-line therapy with either tamoxifen, or doxorubicin and cyclophosphamide (DC). Patients not responding to tamoxifen or DC received second-line therapy with the alternative regimen. Overall, the response rates in the two sequential therapy arms were 43% and 47%, and median survival were 21 months and 18 months, respectively. Similar results were seen in another randomised study in which postmenopausal patients aged over 65 years received either tamoxifen or CMF with crossover on progression of disease. Overall, the response rate was 60% in patients receiving initial tamoxifen and 55% in patients starting with CMF, median survival was 10 months and 8 months, respectively. These studies indicate that endocrine therapy followed by chemotherapy is appropriate, and this is supported by data from another study showing that sequential endocrine therapy/chemotherapy is as effective as the combined approach. Future studies should further analyse the optimal sequence of newer endocrine therapies and chemotherapy [5].

First- and second-line endocrine therapy in postmenopausal patients

Trials conducted before 1990

Testosterone was the first additive systemic therapy for breast cancer and was rapidly followed by high-dose oestrogens, particularly diethylstilboestrol and ethinyloestradiol.

Following the introduction of tamoxifen in the early 1970s, several randomised trials demonstrated a similar activity but less toxicity with this drug compared to the oestrogens [6].

As a consequence, from the early 1980s, tamoxifen became the "gold standard" first-line therapy with progestins and aminoglutethimide as potential candidates for second-line therapies.

From 1980 to 1995, numerous trials were conducted comparing tamoxifen with other endocrine modalities (adrenalectomy, androgens, progestins and aminoglutethimide) and tamoxifen as single agent versus tamoxifen in combination with other endocrine agents (androgens, oestrogens, gestagens and aminoglutethimide) [6].

Conclusions from the trials conducted before 1990

The majority of these trials were quite small and many did not select the patients according to receptor status, as receptor determinations were not generally available at that time. With these reservations, the following conclusions could be drawn from these trials: Tamoxifen remained the preferred first-line therapy; response to first-line therapy predicts the chance of response to second-line therapy; combined endocrine therapies offer no benefit compared to single-agent tamoxifen, emphasising the preference

to use the endocrine agents sequentially. The studies also confirmed the position of progestins and aminoglutethimide as potential candidates for second-line endocrine therapy. In a randomised trial, aminoglutethimide and megestrol acetate demonstrated similar efficacy, although with more pronounced toxicity in the patients treated with aminogluthethimide [7].

Trials conducted since 1990

In the next generation of trials, conducted in the 1990s, the second-line position of aminoglutethimide and progestins was challenged by the second-generation aromatase inhibitor formestane and by the third-generation aromatase inhibitors (exemestane, anastrozole, letrozole), and the first-line position of tamoxifen was challenged by other SERMs and recently by the third-generation aromatase inhibitors.

Second- and third-generation aromatase inhibitors versus aminoglutethimide and megestrol acetate in second-line treatment

Formestane as second-line treatment compared to megestrol acetate (MA) was evaluated in a phase III study enrolling 547 ER^+ or ER-unknown postmenopausal patients suitable for second-line endocrine treatment. Fairly similar median times to treatment failure, progression and overall survival emerged (5 months vs. 5 months, 5 months vs. 6 months, 18 months vs. 20 months, with formestane vs. MA, respectively) but side effects were more pronounced in the MA group [8]. All three third-generation aromatase inhibitors, exemestane, anastrozole and letrozole, were evaluated in the second-line setting, i.e. in patients who had progressed or relapsed on anti-oestrogen therapy.

Exemestane

The phase III trial of exemestane as a second-line therapy was powered to demonstrate equivalence rather than superiority. The trial included 769 postmenopausal women with advanced breast cancer who had progressed with tamoxifen therapy [9]. The patients were randomised to receive exemestane 25 mg once daily or MA 40 mg four times daily (Table 1). Patient demographics in this study were evenly distributed between treatment groups, with over one-half of patients having visceral disease.

Objective response was similar for both agents, as was the rate of stable disease: 21.3% for exemestane and 21.1% for MA. However, exemestane was significantly superior to MA in median time to progression (TTP) ($P = 0.037$). Additionally, at the time of analysis, median survival with exemestane had not been reached, whereas median survival for MA was 123.4 weeks ($P = 0.039$).

Analyses with stratification factors indicated that neither prior chemotherapy nor previous response to tamoxifen was predictive of response to exemestane. However, the site of metastases did significantly correlate to tumour response ($P < 0.0001$). As might be expected, the response rate of patients with tissue disease only was 3.42 times higher than the response rate of patients with visceral metastases (95% confidence interval (CI), 2.07–5.67). Stratified analyses also found that the response rate of patients with visceral disease was 4.55 times higher than the response rate of patients with bone metastases. The investigators suggest that the extremely poor results observed in patients with bone disease may partially be due to difficulty in assessing tumour response in bone.

Patients treated with exemestane had a significantly improved sense of general wellbeing based on a global health status subscale. The most frequently reported side effects in the exemestane and MA groups included hot flushes (13% vs. 5%), weight gain (8% vs. 17%), fatigue (8% vs. 10%), nausea (9% vs. 5%), and increased sweating (5% vs. 8%).

Anastrozole

Anastrozole has been evaluated in two phase III trials, one in North America ($n = 378$) and the other primarily in Europe ($n = 378$) [10]. These trials were powered to demonstrate equivalence. However, in order to "increase the overall statistical reliability of the results, hence making it more likely that a difference would be observed, should one exist", a retrospective decision was made to combine the data from the two trials for the purpose of analysis. Because these trials were designed as equivalence studies and because their data were pooled explicitly for the purpose of

Table 1
Exemestane (Exe) vs. megestrol acetate (MA) as second-line endocrine therapy

Study [Ref.]	Drug, dose	*N*	ORR (%)	TTP (months)	OS (months)
Kaufmann [9]	Exe, 25 mg	366	15.0	4.7	Not reached
	MA, 40 mg × 4	403	12.4	3.9	28.8

ORR, overall response rate; TTP, median time to progression; OS, median duration of overall survival.

strengthening the statistical value, claims of significant superiority based on the published combined analyses must be approached with caution. Together, the North American and the European trials included a total 765 postmenopausal women with advanced breast cancer who had progressed or relapsed with tamoxifen or other anti-oestrogen therapy. Of these, 14% had only soft-tissue metastases, 29% had only bone metastases, 15% had only visceral metastases, 40% had mixed sites, and 3% had no assessable metastatic disease. Patients were randomised to receive 1 mg of anastrozole once daily, 10 mg of anastrozole once daily or 40 mg of MA four times daily (Table 2). Tumour response rates for anastrozole were found to be equivalent to response rates for MA ($P = 0.49$). The rates of stable disease lasting $\geq$6 months were also equivalent, with 29.7%, 27.4% and 28.1% for anastrozole 1 mg, anastrozole 10 mg and MA, respectively. Median time to progression was longer for anastrozole than for MA, but the differences were not significant ($P = 0.30$).

By pooling the data, the investigators were able to find an estimated 2-year survival rate for anastrozole 1 mg (56.1%) that was significantly longer than the estimated 2-year survival rate for MA (46.3%) ($P < 0.025$; 97.5% CI 0.60 to <1.0). However, without the use of retrospective combined analyses, significant survival results were only apparent in the European trial.

All three treatments were generally well tolerated. Treatments were discontinued due to severe adverse drug reactions in 4% of patients treated with MA compared with 2% and 3% of patients treated with anastrozole 1 mg and 10 mg, respectively. Hot flushes occurred in 8%, 13% and 11% and weight gain in 13%, 4% and 3%, respectively.

Recent data from a head-to-head randomised clinical trial of anastrozole versus letrozole in second-line endocrine therapy in patients with hormone receptor-positive or -unknown breast cancer after tamoxifen failure demonstrated higher response rates in the letrozole group (19% vs. 12%, $P = 0.013$). Time-dependent variables, including median duration of response, time to progression and survival, were similar in both groups [11].

In addition, anastrozole was compared with fulvestrant in two multicentre randomised trials, one double-blind conducted in North America (0021) [12] and one open in Australia, South Africa and Europe (0020) [13]. Prospectively, a combined analysis of the two trials was planned. In both trials, the primary endpoint was time to progression and secondary endpoints included response rate, duration of response and tolerability. The results of the studies are presented in Table 3. None of the observed differences are statistically significant. As concerns the primary endpoint, time to progression, for the combined analysis, the hazard ratio is 0.95 (95% CI 0.82–1.10), $P = 0.48$. In conclusion, fulvestrant is at least as effective as anastrozole in the second-line treatment of advanced breast cancer in postmenopausal women with resistance to prior tamoxifen.

The frequency of withdrawals due to drug-related adverse events was 1.2% in the anastrozole-treated group and 0.9% in the fulvestrant group. Hot flushes occurred with similar incidence in the two groups (21% vs. 21.0%), whereas arthralgia occurred significantly more frequently with anastrozole (11% vs. 5%).

Table 2
Anastrozole (Ana) vs. megestrol acetate (MA) as second-line endocrine therapy

Study [Ref.]	Drug, dose	*N*	ORR (%)	TTP (months)	OS (months)
Buzdar [10]	Ana, 1 mg	263	12.5	4.8	26.7
	Ana, 10 mg	248	12.5	5.3	25.5
	MA, 40 mg × 4	253	12.2	4.6	22.5

For explanation of abbreviations, see Table 1.

Table 3
Fulvestant (Fulv) vs. anastrozole (Ana) as second-line endocrine therapy

	Trial 0021 [12]		Trial 0020 [13]		Trials 0021 and 0020 combined	
	Fulv	Ana	Fulv	Ana	Fulv	Ana
N	206	194	222	229	428	423
ORR (%)	17.5	17.5	20.7	15.7	19.2	16.5
CB (%)	42.2	36.1	44.6	45.0	43.5	40.9
TTP (months)	5.4	3.4	5.5	5.1	5.5	4.1

For explanation of abbreviations, see Table 1. CB, rate of clinical benefit.

Letrozole

Letrozole is the only aromatase inhibitor to have been evaluated against aminoglutethimide (AG) as a second-line therapy for advanced breast cancer. In a phase III trial that included 555 postmenopausal women with hormone receptor-positive or -unknown advanced breast cancer who had progressed or relapsed on anti-oestrogen therapy, patients were randomised to receive letrozole 0.5 mg once daily, letrozole 2.5 mg once daily or AG 250 twice daily (Table 4). Visceral disease was the most common predominant metastatic site, and was documented in 44.3%, 48.6%, and 39.9% of patients receiving letrozole 0.5 mg, letrozole 2.5 mg and AG, respectively. The differences between tumour response rates were not statistically significant, but a trend favouring letrozole 2.5 mg over AG was observed with an odds ratio of 1.85 (95% CI, 0.97–3.51; $P = 0.06$). As might be expected, response rates were highest in patients who predominantly had soft-tissue disease, regardless of treatment. In patients who predominantly had bone or visceral metastases, letrozole 2.5 mg produced notably higher response rates (17% for viscera, 17% for bone) than AG (3% for viscera, 9% for bone). Letrozole 2.5 mg was significantly superior to AG with respect to time to progression ($P = 0.003$), and median survival evaluated over a 45-month follow-up was significantly greater with letrozole 2.5 mg than with AG ($P = 0.002$) [14].

Side effects considered to be drug-related occurred more frequently in the group of patients treated with AG than treated with letrozole 0.5 mg and 2.5 mg and included rash (11% vs. 1% vs. 3%), nausea (10% vs. 7% vs. 10%), somnolence (7% vs. 3% vs. 3%) and abdominal pain (5% vs. 1% vs. 2%).

Two randomised, double-blind, multicentre, international trials have compared letrozole with MA. The first of these trials [15] included 551 postmenopausal women with hormone receptor-positive or -unknown, locally advanced, loco-regionally recurrent, or metastatic breast cancer who had failed on previous anti-oestrogen therapy. Approximately 40% of patients had visceral disease and approximately 30% had bone metastases; the majority of patients had only one involved anatomic site. Patients were randomised to receive once-daily doses of letrozole 0.5 mg, letrozole 2.5 mg or MA 160 mg (Table 4).

In this trial, the difference between the response rates of letrozole 2.5 mg and MA was significant ($P = 0.04$), as was the difference between response rates of letrozole 2.5 mg and letrozole 0.5 mg ($P = 0.004$), indicating a dose effect for letrozole. Patients receiving letrozole 2.5 mg demonstrated favourable time-dependent outcome measures. Thus, letrozole 2.5 mg demonstrated a trend towards superiority in median time to progression over MA ($P = 0.07$), and the median survival of 25.3 months achieved by patients treated with letrozole 2.5 mg, was superior to that achieved in both the letrozole 0.5 mg group ($P = 0.03$) and the MA group ($P = 0.15$). This result suggests the possibility of a dose response for letrozole.

A second international trial of letrozole against MA [16] randomised 602 postmenopausal women with hormone receptor-positive or -unknown advanced or metastatic cancer to receive letrozole 0.5 mg, letrozole 2.5 mg or MA 40 mg four times daily (Table 4). Bone disease was documented in 34% of patients receiving letrozole 2.5 mg, compared with 28% of patients receiving the 0.5 mg dose and 26% of patients receiving MA. Visceral disease was documented in approximately 50% of all treatment groups. Patients receiving letrozole had slightly higher response rates than those receiving MA, although the differences were not statistically significant ($P = 0.13$). Significant advantages in time to progression were found with the low dose of letrozole in this trial. Patients receiving letrozole 0.5 mg

Table 4
Letrozole (Letro) vs. aminoglutethimide (AG) vs. megestrol acetate (MA) as second-line endocrine therapy

Study [Ref.]	Drug, dose	*N*	ORR (%)	TTP (months)	OS (months)
Gershanovich [14]	Letro, 0.5 mg	192	16.7	3.3	21
	Letro, 2.5 mg	185	19.5	3.4	28
	AG, 250 mg ×2	178	12.4	3.2	20
Dombernowsky [15]	Letro, 0.5 mg	188	12.8	5.1	21.5
	Letro, 2.5 mg	174	23.6	5.6	25.3
	MA, 160 mg	189	16.4	5.5	21.5
Buzdar [16]	Letro, 0.5 mg	202	20.8	6	33
	Letro, 2.5 mg	199	16.1	3	29
	MA, 40 mg ×4	201	14.9	3	26

For explanation of abbreviations, see Table 1.

had a lower risk of progression than patients receiving MA ($P = 0.044$). A greater median survival favouring letrozole 0.5 mg over MA was not statistically significant, although a strong trend was noted ($P = 0.053$). A careful review of baseline variables for this trial reveals meaningful differences in the site and extent of disease between groups despite randomisation. In particular, patients in the letrozole 2.5 mg treatment arm had the highest rate of bone involvement (34% versus 28% for letrozole 0.5 mg and 26% for MA), a condition usually associated with a poorer prognosis. This situation may relate to the poor performance of patients in the letrozole 2.5 mg arm in this trial and may partially explain why patients in the letrozole 0.5 mg arm fared better.

In both studies weight gain occurred more frequently in the MA-treated patients than in patients treated with letrozole (12% vs. 9%). Other side effects were reported with significantly different frequencies in the two studies. As an example, in the one study [15] hot flushes were reported in 15%, 12% and 12% of patients in the letrozole 0.5 mg, 2.5 mg and in the MA group respectively, whereas in the other study [16], this side effect was reported 5%, 5% and 4% of the similar groups, respectively. Muscoloskeletal disorders were observed in 26–30% of the patients in the one study [15], but in only 1–5% of the patients in the other study [16]. The differences are probably ascribable to differences in questioning and reporting in the different studies and illustrate the difficulties in comparing frequencies of side effects across trials.

In conclusion, all the third-generation aromatase inhibitors have demonstrated superiority in the therapeutic index over aminogluthethimide and megestrol acetate by superiority in one or more efficacy endpoints and a reduced toxicity.

First-line tamoxifen versus other SERMs

Torimifene

Five large phase III randomised controlled trials have been published that have compared toremifene (40 mg to 60 mg) with tamoxifen (20 mg to 40 mg) as first-line endocrine therapy in advanced breast cancer in postmenopausal patients with receptor-positive or -unknown tumours [17]. The response rate to toremifine in these larger multicentre studies was lower than in the phase II studies and ranged from 21 to 38%. In all these studies, toremifene showed equivalent efficacy to tamoxifen for objective response rate, stable disease, time to disease progression, and overall survival. In addition, two of these studies randomised patients between 60 mg toremifene and higher doses (200/240 mg) and found no significant difference in efficacy. There was no difference in drug-related toxicities, and both toremifene and tamoxifen were well tolerated. A recent meta-analysis of 1421 patients from these trials (Table 5) showed a similar response rate for toremifene compared with tamoxifen (24% vs. 25.3%), with no significant difference in the time to disease progression (hazard ratio 0.98, 95% CI 0.87–1.11) or overall survival (hazard ratio 0.98, 98% CI 0.83–1.15) [18].

Table 5
Tamoxifen (Tam) vs. toremifene (Tor) as first-line endocrine therapy[a]

	N	ORR (%)	TTP (months)
Tor	725	24.0	4.9
Tam	696	25.3	5.3

For explanation of abbreviations, see Table 1.
[a] Meta-analysis of five trials [18].

Droloxifene

A randomised dose finding study of 20 mg, 40 mg and 100 mg droloxifene versus tamoxifene in 369 patients as first-line therapy showed objective response rates of 30%, 47% and 44%, respectively, and longer response durations and time to progression was observed with the two higher doses. No significant drug-related toxicities were seen. These first-line data suggested a level of efficacy comparable to that of tamoxifen, and randomised phase III studies comparing droloxifene with tamoxifen were initiated. However, droloxifene was found to be less active than tamoxifen and further development was stopped [17].

Idoxifene

In a phase III trial, 220 postmenopausal women with metastatic breast cancer were randomised to receive either idoxifene 40 mg/day or tamoxifen 20 mg/day as first-line endocrine therapy. Prior adjuvant tamoxifen had been stopped at least 12 months previously and been received by 21% and 14% of the patients, respectively. The objective response rate was 20% (95% CI 12.7–28.2) for idoxifene and 19% (95% CI 12.5–28.2%) for tamoxifen, with a median duration of objective response of 8.1 months for idoxifene and 7.3 months for tamoxifen. In addition, stable disease for $\geq$6 months was observed in 19% of idoxifene- and 29% of tamoxifen-treated patients. Overall, there was no significant difference in time to disease progression or overall survival. Possible drug-related side effects (i.e. hot flushes) were infrequent (<5%) and similar in incidence between idoxifene and tamoxifen. There was no difference

in gynaecological adverse events between idoxifene and tamoxifen. Despite a reduced agonist profile for idoxifene seen in preclinical studies, there appears to be no major difference in terms of clinical efficacy or safety profile between idoxifene and tamoxifen. Further development of the drug was stopped [17].

Raloxifene

Raloxifene demonstrated limited activity in two small phase II trials in advanced breast cancer, but the drug was not developed as an anti-oestrogen for this condition.

Fulvestrant

In a double-blind randomised trial, fulvestrant (200 mg im/month) was compared with tamoxifen (20 mg orally, daily) in the first-line setting [19].

As shown in Table 6, similar efficacy was observed with the two treatments. For the major endpoint, time to progression, the hazard ratio was 1.18 (95% CI 0.98–1.44), $P = 0.088$. In the subpopulation with ER-positive or PgR-positive tumours (79% of the patients randomised to fulvestrant, 77% of patients randomised to tamoxifen), time to progression was 8.2 months and 8.3 months, respectively ($P = 0.388$). In conclusion, fulvestrant is active in the first-line treatment of advanced breast cancer in postmenopausal women with efficacy similar to that of tamoxifen. The tolerability of fulvestrant was very similar to that of tamoxifen and thus, in general, the drug is well tolerated. The most frequent drug-related side effect included hot flushes (approximately 20% of patients) and muscoloskeletal disorders.

In conclusion, none of the SERMs have proved to offer significant advantages over tamoxifen in the first-line management of breast cancer. Accordingly, tamoxifen remains the first-line reference treatment of choice to be used as a comparator against potential new endocrine agents.

First-line tamoxifen vs. aromatase inhibitors

In the first-line setting, i.e. in patients with no prior exposure to tamoxifen in the advanced breast cancer situation or who had terminated adjuvant anti-oestrogenic therapy at least 1 year previously, a second-generation aromatase inhibitor (formestane) and all the third-generation aromatase inhibitors were compared with tamoxifen.

Table 6
Tamoxifen (Tam) vs. fulvestant (Fulv) as first-line endocrine therapy

Study [Ref.]	Drug	*N*	ORR (%)	CB (%)	TTP (months)
Robertson [19]	Tam	313	33.9	62.0	8.3
	Fulv	274	31.6	54.3	6.8

For explanation of abbreviations, see Tables 1 and 3.

Formestane

Formestane as first-line treatment compared to tamoxifen was evaluated in a phase III trial in 409 patients with receptor-positive tumours. Response rates and survival were equal (28% vs. 31% and 32 months vs. 33 months for formestane and tamoxifen, respectively), but time to progression was longer with tamoxifen [20]. Based on efficacy and tolerability, tamoxifen remained first-line treatment.

Exemestane

Preliminary data from a randomised phase II study of exemestane evaluated against tamoxifen has been presented [21]. In the 120 patients enrolled, preliminary evaluation of tolerability showed both agents to be well tolerated. Overall response rates using an intent to treat analysis were 44.6% for exemestane (5 CR, 20 PR) and 14.3% for tamoxifen (1 complete response (CR), 7 partial response (PR)) whereas stable disease was observed in 10.7% of patients treated with exemestane and 25% of those treated with tamoxifen. These preliminary data suggest that exemestane is active in previously untreated hormone receptor-positive or unknown metastatic breast cancer, but comparison with tamoxifen requires data from the ongoing randomised phase III study.

Anastrozole

Two phase III trials of anastrozole as a first-line therapy of advanced breast cancer, one in North America, trial 030 ($n = 353$) and the other in Europe, Australia, New Zealand, South Africa, South America (Rest of the World), trial 027 (N-668), have been conducted [22,23]. Both trials were double-blind/double-dummy and randomised postmenopausal women with advanced breast cancer suitable for endocrine therapy to receive either once-daily anastrozole 1 mg or once-daily tamoxifen 20 mg. The primary endpoints were time to progression, response rate and tolerability and secondary endpoints included time to treatment failure, time to progression in responding patients and overall survival. Both studies were powered to demonstrate equivalence in endpoints. The studies were designed to be combined, and recruitment stopped in the American trial when the prespecified number of patients had been randomised in the Rest of the World trial.

Within the two trials, the patient characteristics

Table 7
Anastrozole (Ana) vs. tamoxifen (Tam) as first-line endocrine therapy

Study [Ref.]	Drug	*N*	ORR (%)	CB (%)	TTP (months)	OS (months)
Nabholtz [22]	Ana	171	21.1	59.1	11.1	33
	Tam	182	17.0	45.6	5.6	32
Bonneterre [23]	Ana	340	32.9	56.1	8.2	38
	Tam	328	32.6	55.5	8.3	40
Bonneterre [24]	Ana	511	29.0	57.2	8.5	
	Tam	510	27.1	52.0	7.0	

For explanation of abbreviations, see Tables 1 and 3.

were evenly distributed, but between the two trials, major differences in characteristics were apparent. Thus among patients randomised to anastrozole 21% of patients in the North American trial had received prior adjuvant endocrine therapy compared to 12% of the patients in the Rest of the World trial. A larger proportion of patients (88%) in the American trial had tumours known to be receptor-positive compared to 45% in the other trial. Also the distribution of the dominant site differed between the 2 trials: the dominant site was soft tissue in 11%, bone in 40% and viscera in 49% of the patients in the American trial compared to 38%, 31% and 30% respectively in the Rest of the World trial. The efficacy data are presented in Table 7. In the North America trial, median time to progression was significantly in favour of anastrozole ($P = 0.005$). In a retrospective analysis, the rate of clinical benefit, which was not a predefined endpoint, was also superior in patients treated with anastrozole ($P = 0.0098$). No significant differences were observed for the other primary endpoint, response rate, nor for survival. In the Rest of the World trial, no significant differences were observed for any of the 3 endpoints, time to progression, response rate, median duration of survival, nor in the rate of clinical benefit.

A recent publication analysed the combined data of the two anastrozole trials [24]. Combining the two trials resulted in patients characteristics very similar to the characteristics of the letrozole trial and no significant differences were observed for any of the major endpoints (Table 7), time to progression and response rate nor for clinical benefit. A retrospective subgroup analysis suggested significant superiority with anastrozole in the subgroup of patients with tumours known to be receptor-positive ($P = 0.022$), but time to progression was similar in other subgroups of patients with or without prior adjuvant anti-oestrogen therapy, in patients more than 65 years of age or younger and in subgroups with or without bone lesions only, visceral lesions or liver lesions.

In the two trials, both drugs were well tolerated. Adverse effects were reported irrespective of causality. In the North American trial, hot flushes were observed in 38% of patients treated with anastrozole compared to 28% patients treated with tamoxifen. Other side effects included nausea (30% vs. 34%), thromboembolism (4% vs. 8%) and weight gain (3% vs. 1%). In the Rest of the World trial, hot flushes occurred in 21% vs. 21% of the patients, nausea in 13 vs. 13%, thromboembolism in 5% vs. 7%, and weight gain in 2% vs. 2%.

In conclusion, anastrozole has demonstrated at least equivalence with tamoxifen in first-line endocrine therapy for advanced breast cancer.

Letrozole

The largest prospective study of a first-generation aromatase inhibitor as first-line therapy was an international trial that included 907 postmenopausal women suitable for endocrine therapy who were randomised in a double-blind, double-dummy designed study to receive either once-daily letrozole 2.5 mg or once-daily tamoxifen 20 mg [25]. An integral part of the study was optional cross-over at the time of progression when patients considered suitable by the investigators for second-line endocrine therapy were crossed-over to the alternative therapy, i.e. patients with progression on letrozole were switched over to tamoxifen and vice versa. The primary endpoint was time to progression and the study was powered for superiority. Secondary endpoints included rates and durations of overall response and clinical benefit, time to treatment failure, overall survival and tolerability. Baseline characteristics were evenly distributed in the two arms. Two thirds of the patients had tumours known to be receptor-positive and approximately 20% had had prior adjuvant anti-oestrogen therapy. Data at the 18-month follow-up are presented in Table 8. Letrozole demonstrated statistically significant superiority to tamoxifen for the primary efficacy endpoint, time to progression, with a median of 9.4 months, compared with 6 months for tamoxifen ($P = 0.0001$). Moreover, prospectively planned stratified analyses of key baseline covariates showed that treatment with letrozole was significantly more favourable than tamoxifen in all analysed subgroups, i.e. irrespective of receptor status (positive or unknown), prior anti-oestrogen therapy or site of dominant disease.

Letrozole was also shown to be statistically superior to tamoxifen in terms of the secondary efficacy endpoints, rate of response ($P = 0.0002$) and clinical benefit ($P = 0.0004$).

Table 8
Letrozole (Letro) vs. tamoxifen (Tam) as first-line endocrine therapy

Study [Ref.]	Drug	*N*	ORR (%)	CB (%)	TTP (months)	OS (months)
Mouridsen [25]	Letro	453	32.0	49.9	9.4	34
	Tam	454	20.9	38.1	6.0	30

For explanation of abbreviations, see Tables 1 and 3.

There was no significant difference between median duration of survival amongst the two groups ($P = 0.5303$). However, a prospectively planned analysis at 6 monthly intervals demonstrated a significant survival advantage for letrozole during the first 2 years following study entry [26]. At 12 and 24 months respectively 83% and 64% of patients randomised to letrozole were still alive compared with 75% and 58% respectively of patients randomised to tamoxifen. Also in this trial, both drugs were well tolerated. Most frequent drug-related adverse events included hot flushes (16% of the patients treated with letrozole compared with 13% of patients treated with tamoxifen), nausea (6% vs. 6%), and hair-thinning (5% vs. 3%).

In conclusion, letrozole has demonstrated significant superiority in efficacy over tamoxifen in the first-line endocrine therapy for advanced breast cancer.

One trial compared quality of life in patients randomised to treatment with either anastrozole or letrozole. This study indicated superiority with letrozole in the quality of life estimates and significantly more patients preferred to continue with letrozole in the subsequent open labelled treatment with the aromatase inhibitor [27].

Treatment of advanced breast cancer in premenopausal patients

Indirect comparisons of cumulative data indicate similar response rates after oophorectomy, tamoxifen or LHRH analogue therapy [7], and the equivalence of these three endocrine treatment regimes has been confirmed in randomised trials, two comparing oophorectomy with tamoxifen, one comparing LHRH analogue treatment with surgical oophorectomy and one comparing LHRH analogue treatment with tamoxifen [28]. However, these trials were all very small and powered to demonstrate only very large differences. Four trials compared LHRH analogues alone with the combined treatment of tamoxifen and an LHRH analogue and were included in a meta-analysis [29]. As shown in Table 9, the combined therapy approach was significantly superior for all the major endpoints. In view of these data, the combined approach of tamoxifen and ovarian suppression should now be considered the standard therapy for premenopausal patients for whom endocrine therapy is indicated.

The role of aromatase inhibitors in premenopausal patients is still an area of research. Given as single agents, the suppression of oestrogens will result in a compensatory increase of gonadotrophins, with induction of ovarian hyperstimulation and upregulation of the aromatase enzyme, which will partly overcome the aromatase inhibition [30]. Its role in combination with ovarian suppression needs to be evaluated further.

Conclusions

Endocrine therapies are widely used to treat patients with advanced breast cancer. Response to endocrine therapies depends largely on the presence and sensitivity of tumour hormone receptors. Tamoxifen has been the "gold standard" of endocrine therapy for the first-line treatment of receptor-positive postmenopausal women for over 20 years, with progestin and aminoglutethimide as options for second-line therapy. Recent results from several large, randomised, double-blind, multicentre trials have significantly changed this treatment algorithm. Thus, aromatase inhibitors can be at least as effective and,

Table 9
Meta-analysis of four trials with LHRH analogue (LHRH) vs. the combination of LHRH analogue and tamoxifen (LRHR + Tam)

Study [Ref.]	Drug	*N*	ORR (%)	TTP (months)	OS (months)
Klijn [29]	LHRH	256	29.7	5.4	2.5
	LHRH + Tam	250	38.8	87	2.9
Hazard/odds ratio (95% CI)			0.67 (0.46–0.96)	0.70 (0.58–0.85)	0.78 (0.63–0.96)
P-value			0.03	0.003	0.02

For explanation of abbreviations, see Table 1.

in some cases, clearly superior to previously used second-line therapies. These data combined with a better safety profile than progestins and aminogluthethimide has facilitated the acceptance of aromatase inhibitors as appropriate therapy for second-line treatment of metastatic disease after tamoxifen failure.

The position of tamoxifen as the "gold standard" of first-line therapy has been challenged by newer SERMs with a higher antagonist/agonistic ratio than tamoxifen, but these have failed to demonstrate superiority over tamoxifen. However, first-line evaluation against tamoxifen has demonstrated that non-steroidal aromatase inhibitors are at least as effective (anastrozole) as this agent or clearly superior (letrozole) in outcome measures.

In the future, an increasing proportion of patients will present with metastatic disease following or while on adjuvant tamoxifen. Following first-line treatment of advanced disease with non-steroidal third-generation aromatase inhibitors, the optimal second-line therapy to be offered to patients still suitable for endocrine therapy needs to be defined among the treatment options available today, including exemestane, fulvestrant and progestins.

Also the optimal sequence of aromatase inhibitors with chemotherapy and receptor-positive metastatic disease needs to be re-evaluated. In the premenopausal patients recent data have indicated that past therapies of either tamoxifen or ovarian suppression should be substituted by the combination of the two. The role of aromatase inhibitors in this setting remains to be defined.

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