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The sequential use of endocrine treatment for advanced breast cancer: where are we?

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Background: Hormone receptor-positive advanced breast cancer is an increasing health burden. Although endocrine therapies are recognised as the most beneficial treatments for patients with hormone receptor-positive advanced breast cancer, the optimal sequence of these agents is currently undetermined.
Methods: We reviewed the available data on randomised controlled trials (RCTs) of endocrine therapies in this treatment setting with particular focus on RCTs reported over the last 15 years that were designed based on power calculations on primary end points.
Results: In this paper, data are reviewed in postmenopausal patients for the use of tamoxifen, aromatase inhibitors and fulvestrant. We also consider the available data on endocrine crossover studies and endocrine therapy in combination with chemotherapy or growth factor therapies. Treatment options for premenopausal patients and those with estrogen receptor-/human epidermal growth factor receptor 2-positive tumours are also evaluated.
Conclusion: We present the level of evidence available for each endocrine agent based on its efficacy in advanced breast cancer and a diagram of possible treatment pathways.
Key words: advanced breast cancer, algorithm, endocrine, hormone receptor positive, postmenopausal, treatment pathway

introduction

Despite early diagnosis and improving treatment options for primary breast cancer, there continues to be a substantial number of women who relapse with advanced disease. Approximately 80% of breast cancer cases in Western countries are estrogen receptor positive (ER+) [1] and for the majority of these patients, endocrine therapy is an appropriate option in both the adjuvant and advanced setting. This manuscript reviews the available data on randomised controlled trials (RCTs) of endocrine therapies in the treatment of hormone receptor-positive (HR+) advanced breast cancer.

HR+ postmenopausal patients with advanced breast cancer

Before contemporary phase III trials involving third generation aromatase inhibitors (AIs), RCTs were much smaller in size and were seldom prospectively powered to test for either superiority or equivalence between the two arms. Indeed, assumptions were made that different endocrine agents such as tamoxifen, megestrol acetate (MA) and aminoglutethimide had equivalent efficacy (but different side-effect profiles) based on small datasets where type 2 errors were a distinct possibility.

tamoxifen versus high-dose estrogens

Tamoxifen is a selective ER modulator (SERM), which antagonises estrogen signalling in the treatment of HR+ advanced breast cancer. The high-dose estrogens were known to be effective in breast cancer treatment, possibly by increasing p53 levels [2]. A review of RCTs comparing tamoxifen with high-dose estrogens reported that overall response rates (ORRs) were comparable (33% versus 31%) [3]. In the initial report of diethylstilbestrol (DES) compared with tamoxifen ($n = 143$), there were also no differences observed in time to treatment failure, duration of response or overall survival (OS) [4]. Although, a subsequent update reported that survival was significantly longer with DES [5], tamoxifen became the initial

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endocrine therapy of choice due to its improved side-effect profile.

tamoxifen versus MA

MA is thought to treat breast cancer by inhibiting pituitary function and thus suppressing luteinising hormone and the subsequent production of estrogen. In at least five RCTs [6–11], tamoxifen was shown to have comparable efficacy with MA in terms of ORR and OS and a better side-effect profile.

tamoxifen versus SERMs

Tamoxifen has also been tested against several other SERMs. Analyses have shown that tamoxifen was comparable to toremifene ($n = 1421$) [12] or idoxifene ($n = 220$) [13] and was superior to droloxifene [ORR ($P = 0.02$) and time to progression (TPP) ($P < 0.001$)] [14] and to arzoxifene [progression-free survival (PFS; $P = 0.01$)] [15].

Overall, tamoxifen was therefore deemed to be as good as, or better than, all alternative SERMs with phase II crossover studies showing cross-resistance between tamoxifen and other SERMs.

tamoxifen versus first- and second-generation AIs

AIs are thought to work by inhibiting aromatase signalling, which ultimately blocks the estrogen receptor. The first-generation AI aminoglutethimide was shown to be comparable with tamoxifen alone [16, 17] or with aminoglutethimide plus tamoxifen [18, 19]. The latter trials are among the first to study an AI in combination with an antiestrogen and no improvement was observed over the antiestrogen alone.

tamoxifen versus other endocrine agents (meta-analysis)

Fossati et al. [20] reviewed 35 RCTs comparing tamoxifen with a range of other endocrine therapies, including ovarectomy, MA, AIs, medroxyprogesterone acetate, SERMs, goserelin and fluoxymesterone. They reported an ORR of 30% with tamoxifen versus 29% with the other agents and an OS hazard ratio of 1.02 [confidence interval (CI) 0.94–1.10].

Tamoxifen became the standard therapy for advanced breast cancer, having demonstrated first-line efficacy when compared with a range of other endocrine agents in advanced breast cancer.

third-generation AIs: anastrozole and letrozole (competitive, non-steroidal) and exemestane (non-competitive, steroidal) versus MA as second-line endocrine therapy

These trials were the first endocrine therapy RCTs prospectively powered to demonstrate significant differences in clinical outcome(s). Anastrozole showed no significant difference in TTP from MA on an initial analysis [21, 22]. However, a planned subsequent analysis found anastrozole 1 mg o.d. to be associated with significantly increased OS versus MA (median 26.7 versus 22.5 months, respectively; $P < 0.025$) [23]. Two studies of letrozole 2.5 mg o.d. versus MA showed no significant difference in TTP or OS [24, 25]. Exemestane resulted in an increased TTP (4.7 versus 3.8 months; $P = 0.037$) and a significantly longer OS (median OS not reached for exemestane at time of publication versus 28.5 months for MA; $P = 0.039$) compared with MA [26]. AIs were initially introduced based on the improved side-effect profile but similar TTP versus MA. Subsequently, this decision was supported by the OS data with anastrozole and the increased efficacy seen with exemestane.

third-generation AIs: anastrozole and letrozole (competitive, non-steroidal) and exemestane (non-competitive, steroidal) versus tamoxifen as first-line endocrine therapy

Anastrozole was shown to be superior to tamoxifen in terms of TTP in a North American-based trial where almost 90% of patients were known to be HR+ [27]. No significant difference in TTP was reported in TARGET, a 'Rest of the World' study. However, only 45% of patients in TARGET were known to have an HR+ tumour [28]. In a pooled retrospective analysis of the two trials including patients with known HR+ tumours, anastrozole was shown to be superior to tamoxifen for TTP but not for OS [29]. Letrozole significantly prolonged TTP compared with tamoxifen but, again, no significant difference in OS was observed [30]. Exemestane had similar PFS and OS compared with tamoxifen using the log-rank test; when PFS was assessed using the Wilcoxon test, it was significantly longer with exemestane than tamoxifen [31].

Overall, the third-generation AIs were deemed more effective in terms of disease control than MA and tamoxifen and were well tolerated and so have become the preferred first-line endocrine therapy. This finding is similar to the adjuvant settings, where third-generation AIs have been compared with tamoxifen in large trials [32–35].

Fulvestrant: 250 mg dose

Fulvestrant is a selective ER down regulator (SERD) that binds, blocks and increases degradation of ER, resulting in inhibition of estrogen signalling [36]. It was initially approved at a dose of 250 mg/month after studies showed that it was as effective as anastrozole 1 mg/day in the treatment of HR+ advanced breast cancer in the second-line setting, after tamoxifen [37].

Fulvestrant: 500 mg dose

Fulvestrant 500 mg was compared with fulvestrant 250 mg in a phase III RCT in the second-line setting in women with advanced breast cancer in the CONFIRM study. The primary end point TTP was significantly longer for patients receiving fulvestrant 500 mg versus fulvestrant 250 mg

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(hazard ratio = 0.80; $P = 0.006$). The difference in OS did not reach statistical significance ($P = 0.091$) at the initial analysis [38]. This finding is fully consistent with the increased biological effects seen with the 500 mg dose compared with 250 mg [39].

Fulvestrant 500 mg was also compared with anastrozole 1 mg/day in the metastatic setting in the phase II FIRST trial ($n = 205$). TTP was significantly prolonged with fulvestrant 500 mg (hazard ratio = 0.626; $P = 0.0496$) [40]. Adverse events were comparable between treatment arms. Data from the FIRST study showed that the significant difference in TTP had persisted with longer follow-up (23.4 months with fulvestrant versus 13.1 months with anastrozole; hazard ratio = 0.66; $P = 0.01$) [41].

In summary, fulvestrant 500 mg has a biologically greater effect and provides a clinically meaningful benefit over fulvestrant 250 mg. The standard dosing schedule of fulvestrant should now be 500 mg and, based on its increased efficacy, should be considered earlier in the treatment of advanced disease.

endocrine crossover studies

In contrast with the comparative wealth of data from head-to-head studies, there are only two RCTs assessing the impact of treatment sequence. In a first-line study, letrozole 2.5 mg was associated with longer initial TTP than tamoxifen 20 mg (9.4 versus 6.0 months; $P = 0.0001$); yet, there was no significant difference in survival [30].

In a 60-patient subgroup of the TARGET study, time to first progression was 11.3 months with anastrozole and 8.3 months with tamoxifen [42]. The time from randomisation to second progression was 28.2 months for patients who started on anastrozole and crossed over to tamoxifen and 19.5 months for the opposite regimen. However, the study is not sufficiently powered to draw conclusions.

Although there is a scarcity of data from robust RCTs, the available non-randomised data regarding the effects of endocrine sequence demonstrate that response to first-line therapy predicts for response to subsequent endocrine therapy [43, 44]. However, there are no data showing that one treatment sequence is preferable to another.

endocrine therapy plus chemotherapy

According to accepted convention, the concomitant use of chemotherapy and hormonal therapy is not recommended in the treatment of breast cancer, as the two mechanisms are considered theoretically to be antagonistic.

The Australian and New Zealand Breast Cancer Trials Group evaluated doxorubicin 50 mg/m^2 plus cyclophosphamide 750 mg/m^2 in sequence, and in combination, with tamoxifen 20 mg b.i.d. ($n = 339$). As patients were not selected based on HR status, it is not surprising that the response rates were variable between groups. However, TTP was not significantly different and OS was almost identical, irrespective of treatment sequence [45].

Tominaga et al. [46] reported that MA in combination with cyclophosphamide, doxorubicin and fluorouracil (CAF) chemotherapy was better than CAF alone. However, this design is chemotherapy with or without endocrine therapy (in an HR unknown population) rather than endocrine therapy with or without chemotherapy in HR+ advanced breast cancer.

Overall, clinical trials in this area are lacking, particularly with combinations of the newer classes of endocrine agents such as AIs or SERD (fulvestrant) with or without chemotherapy.

the treatment of ER+/human epidermal growth factor receptor 2-positive postmenopausal patients with advanced breast cancer

Although a notable proportion of patients with breast cancer have human epidermal growth factor receptor 2-positive (HER2+) tumours, there are currently no definitive data on when to use anti-HER2 agents and hormone therapy in the advanced breast cancer setting. However, some studies have been conducted in these patients.

The addition of trastuzumab or lapatinib to AI therapy, anastrozole or letrozole, respectively, has shown clinical benefit for patients with tumours that were HR+/HER2+. In both studies, addition of the growth factor inhibitor improved clinical benefit rate (CBR) and PFS but there was no significant difference in OS ($P = 0.325$ for trastuzumab [47, 48]; not reported for lapatinib [49]).

To date, there are no studies comparing endocrine therapy with chemotherapy in this setting [50].

Fulvestrant with or without lapatinib was evaluated in a phase III study in patients with HR+ advanced breast cancer. At the third interim analysis, no improvements were observed in PFS or OS with the addition of lapatinib to fulvestrant. However, in patients with HER2+ tumours, a trend towards improved PFS was observed (5.9 versus 2.8 months for fulvestrant + lapatinib versus fulvestrant alone; $P = 0.29$). Treatment was generally well tolerated [51].

In all of these studies, the data suggest that the addition of a HER2-targeted therapy increased the efficacy of the endocrine agent by almost doubling both CBR and TTP. There are no RCT comparisons of the combination versus the anti-HER2 therapy alone. Whether an individual patient receives combination of endocrine and HER2-targeted therapies or an endocrine therapy alone is a decision for each patient and their physician [52].

combined endocrine and growth factor therapies

Cristofanilli et al. [53] reported prolonged PFS with anastrozole plus gefitinib ($n = 43$) versus anastrozole plus placebo ($n = 50$; HR = 0.55; 95% CI 0.32–0.94) in postmenopausal women with HR+ metastatic breast cancer. This, however, was not reflected in the neoadjuvant RCT of anastrozole versus anastrozole plus gefitinib [54]. In a study of tamoxifen with or without gefitinib, no PFS benefit was reported with the addition of gefitinib to tamoxifen [55].

In a phase III trial, letrozole plus temsirolimus offered no PFS advantage over letrozole alone in ER+ metastatic breast cancer [56]. However, in a randomised phase II trial of 111 patients with HR+ and HER2-negative tumours and with prior exposure to AIs, tamoxifen with everolimus was superior to

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tamoxifen alone in terms of CBR (61.1% versus 42.1%) and median TTP (8.5 versus 4.5 months; $P = 0.008$, exploratory analysis) [57]. The mTOR inhibitors warrant further clinical evaluation in combination with endocrine therapies, particularly SERMs.

In a randomised phase II study ($n = 156$), the addition of the monoclonal IGF-1 receptor antibody antagonist AMG 479 to exemestane or fulvestrant provided no additional PFS benefit for patients with HR+ metastatic or locally advanced breast cancer [58].

It has been suggested that therapies targeted at growth factor signalling may help to overcome acquired resistance to endocrine therapy. However, current data are lacking and further, robust clinical investigations are required.

the treatment of HR+ premenopausal patients with advanced breast cancer

In premenopausal patients, ovarian ablation has been the standard treatment for over 100 years [59, 60]. Ovarian ablation [oophorectomy, radiotherapy, luteinising hormone-releasing hormone agonists (LHRHa)] with or without tamoxifen perhaps remains the most common initial therapeutic endocrine choice in premenopausal women. However, tamoxifen has been shown to be an effective monotherapy agent too.

Tamoxifen is approved for the treatment of premenopausal patients with ER+ advanced breast cancer, and two small RCTs have shown that it has comparable efficacy (in terms of response rates and OS) to oophorectomy [61, 62]. Goserelin, an LHRHa, is recognised as an effective alternative to oophorectomy in pre/perimenopausal women following phase III evaluation [61, 63, 64]. In a meta-analysis of four studies by Klijn et al. [65] ($n = 506$), the combination of LHRHa plus tamoxifen resulted in significantly prolonged PFS ($P < 0.001$) and OS ($P = 0.02$) relative to either agent alone.

Of note, in the largest of these studies, combination therapy was compared with sequential therapy. Although the TTP was longer for the combination, there was no difference between the two arms in terms of 'time to total failure' (Unpublished data; AstraZeneca on file).

AIs are not suitable for use alone in premenopausal women due to the high oestradiol levels in these patients; AIs must therefore be used in combination with ovarian suppression. Fulvestrant 250 mg has not been evaluated as a sole therapy in premenopausal women with advanced breast cancer but fulvestrant 250 mg in combination with goserelin has been reported to have a CBR rate of 45% in premenopausal patients ($n = 20$) [50].

In summary, there are no firm data to suggest that ablation of ovarian function in premenopausal women renders them equivalent to postmenopausal patients, but until any other data become available, this appears the most logical therapeutic approach and current trials have shown some degree of success.

discussion

In many of the key studies reported to date, observed improvements in TTP did not translate into OS improvements. Therefore, how do we weight end points—i.e. CBR compared with TTP compared with OS? (Figure 1). Furthermore, the relevance of an end point depends on the mechanism of action of the treatment. For example, ORRs may not be appropriate for agents that slow or delay disease progression. Therefore, it is particularly important to select end points appropriately for studies in advanced breast cancer.

With endocrine therapy, prior response predicts the likelihood of subsequent response to another endocrine agent, and this should be taken into account when assessing whether to prescribe a subsequent endocrine therapy. However, for individual patients the duration of control beyond 6 months on one endocrine therapy does not predict for the duration of control beyond 6 months on a subsequent endocrine therapy. This fact suggests that individual tumours respond differently to different endocrine agents and that being able to select which endocrine agent an individual patient's tumour is most sensitive to is a realistic, as well as a clinically worthwhile, goal.

Treatment is continued until patients experience clinical disease progression, assuming the absence of serious adverse events. Stopping endocrine therapy is not recommended in advanced breast cancer, although some specific occasions do arise where the physician and patient may agree to this approach. It would seem worth testing intermittent endocrine therapy in future trials. This could either be with a single agent or involve multiple agents used in rotation in a predefined or randomly assigned sequence, with the aim of stopping or delaying the development of tumour resistance. There are limited data suggesting a degree of further benefit in individuals re-exposed to the same endocrine agent. Most data in this setting are with tamoxifen but it is all non-randomised. While it is not poor practise to reintroduce a prior treatment in a patient who previously responded, it is often not the best therapeutic option unless all endocrine options have been exhausted.

The paucity of data from RCTs of sequencing of endocrine therapies in patients with advanced breast cancer means that no

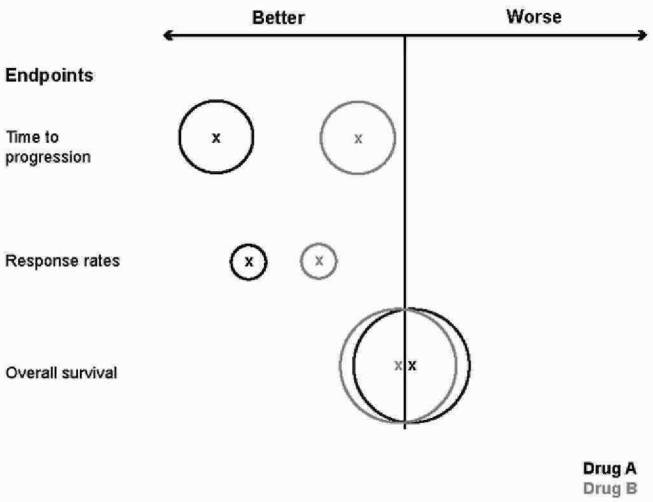

Figure 1. Comparison of properties of drug A versus drug B. Which drug would you choose? Schematic representation of different potential end points and the level of 'weight' assigned to them. X represents the score assigned for each drug for each end point. The circles represent the amount of 'weight' one might assign to each end point. Consider how your opinion of drug A versus drug B would change if the locations of the markers moved.

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definitive recommendations can be made. There are few RCTs that have compared the same sequence of two drugs given in the opposite order: the study with letrozole and tamoxifen provides the most robust data in this setting [30]. The most reliable evidence currently available for possible sequences is provided by head-to-head trials that have been conducted in second- or third-line settings where the patients' prior therapies are known and the therapies are proven to be effective in patients in that treatment setting. No trials have been conducted that specifically compared different combinations of endocrine agents in sequence. We have, therefore, prioritised selection of endocrine agents based on their known efficacy in this particular setting of advanced breast cancer. We have highlighted the level of evidence (Figures 2 and 3).

treatment selection

postmenopausal patients

first line. For first-line treatment in advanced breast cancer, a non-steroidal AI is the standard choice, although there seems little to differentiate between anastrozole and letrozole in this setting. The phase II data of fulvestrant 500 mg versus an AI (anastrozole) in the first-line setting showed a significant advantage for fulvestrant 500 mg. Considering the long-term follow-up, fulvestrant has become a therapeutic option in this setting, especially if there is a contraindication to AIs or a problem with compliance. While some clinicians in some countries may accept the phase II data as being sufficient for this treatment option, a phase III study of first-line fulvestrant 500 mg versus AIs is recommended to fully understand the potential benefits.

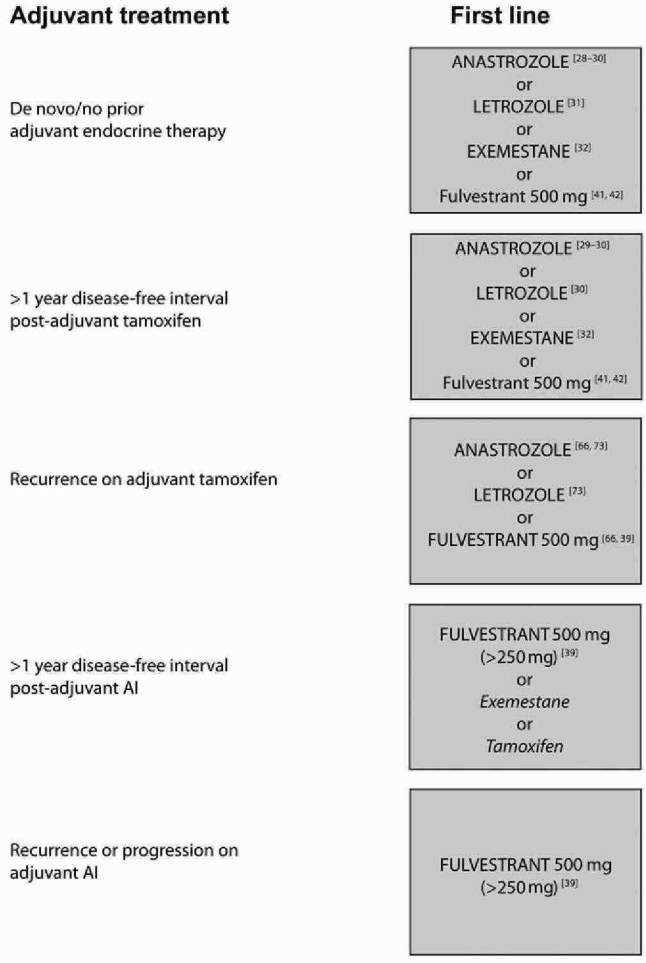

Figure 2. Recommended order of selection of first-line endocrine agents in various therapeutic settings, based on level of evidence available.

With non-steroidal AIs being widely used in the adjuvant setting, the choice of a different endocrine agent for first-line advanced disease has to be considered. In the CONFIRM trial, all patients were receiving a second hormone therapy, and fulvestrant 500 mg was superior to fulvestrant 250 mg in terms of the primary end point, TTP. Approximately half the patients were treated after adjuvant endocrine therapy and half after endocrine therapy for advanced disease. Approximately half of the patients had received prior AI and half prior tamoxifen. In the absence of other RCT data, fulvestrant 500 mg would appear to have the most RCT data in the post-adjuvant AI setting.

There are non-randomised data that show that tumours will respond to other endocrine agents in the post-AI setting (e.g. exemestane, tamoxifen, MA), but these are selected datasets and are not obtained from RCTs.

second line. In studies of second-line endocrine therapy for advanced disease, the third-generation AIs were considered superior to progestins [23–26]. The main benefits, which led to initial regulatory approval, involved safety: absence of significant weight gain and reduction of dyspnoea observed with MA [23, 26]. Survival benefits for non-steroidal AIs were seen on long-term follow-up with anastrozole [23]. However, as non-steroidal AIs are now used much earlier, other endocrine agents should be considered for second line [67]. Similar second-line data are available for exemestane.

Fulvestrant 250 mg is equivalent to AIs in the second-line setting in terms of TTP and OS. Similar results were seen in two large phase III studies (studies 20 and 21) of parallel design [3, 68], which were then combined in a prospectively planned overview analysis [37]. In this study, 99% of patients had received tamoxifen as their prior endocrine therapy. Recently, fulvestrant 500 mg has been shown to be superior to fulvestrant 250 mg in the second-line setting after failure of antiestrogen therapy [38]. In this study, 57.5% of patients had received prior tamoxifen and 42.5% had received a prior non-steroidal AI. The hazard ratio for PFS was 0·8 ($P = 0.006$) with a trend towards OS ($P = 0.09$) on the first data analysis. These findings are consistent with data from the phase II RCT in the first-line setting, which showed that fulvestrant 500 mg had greater efficacy than anastrozole.

In terms of post-AI in advanced disease, the EFECT study reported no difference between fulvestrant 250 mg and exemestane. Again, since CONFIRM subsequently reported that fulvestrant 500 mg was superior to 250 mg, this provided an indirect comparison between fulvestrant 500 mg and exemestane post-AI given in the advanced setting.

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