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Review

Endocrine treatment options for advanced breast cancer – the role of fulvestrant

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Abstract

For many years, tamoxifen has been the 'gold standard' amongst anti-oestrogen therapies for breast cancer. However, the selective aromatase inhibitors (AIs), anastrozole, letrozole and exemestane, have demonstrated advantages over tamoxifen as first-line treatments for advanced disease. Anastrozole is also more effective as an adjuvant treatment in early, operable breast cancer and is being increasingly used in the adjuvant setting. Generally, the selective oestrogen receptor modulators (SERMs), such as toremifene, droloxifene, idoxifene, raloxifene, and arzoxifene, show minimal activity in tamoxifen-resistant disease and show no superiority over tamoxifen as first-line treatments. In addition to these agents, other treatment options for advanced disease include high-dose oestrogens and progestins. Response rates for high-dose oestrogens and tamoxifen are similar, but the use of oestrogens is limited by their toxicity profile. Consequently, there is a need for new endocrine treatment options for breast cancer, particularly for use in disease that is resistant to tamoxifen or AIs. Fulvestrant ('Faslodex') is a new type of steroidal oestrogen receptor (ER) antagonist that downregulates cellular levels of the ER and progesterone receptor and has no agonist activity. This paper reviews the key efficacy and tolerability data for fulvestrant in postmenopausal women in the context of other endocrine therapies and explores the potential role of fulvestrant within the sequencing of endocrine therapies for advanced breast cancer.

Keywords: Advanced breast cancer; Treatment; Fulvestrant; Faslodex; Postmenopausal

1. Introduction

Fulvestrant ('Faslodex') is a new type of endocrine agent, an oestrogen receptor (ER) antagonist that has no agonist effects. It downregulates cellular levels of the ER, resulting in the decreased expression of the progesterone receptor (PgR). This paper reviews key efficacy and tolerability data for fulvestrant in the context of other endocrine therapies and explores the potential role of fulvestrant within the sequence of endocrine agents used for treating postmenopausal women with advanced breast cancer.

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2. SERMs, oestrogens and ER downregulators

Tamoxifen is a non-steroidal triphenylethylene agent that has been the 'gold standard' selective oestrogen receptor modulator (SERM) amongst anti-oestrogen therapies since the 1970s. Tamoxifen is an oestrogen antagonist in breast tissue, but acts as an oestrogen agonist in the bones and endometrium. This spares bone mineral density and serum cholesterol levels from the full effects of oestrogen deprivation [1,2], but is also associated with undesirable side effects such as an increased risk of endometrial cancer and thromboembolic events [3]. The selective aromatase inhibitors (AIs), anastrozole, [4,5] letrozole [6,7] and exemestane [8], have since been shown to have advantages over tamoxifen as first-line treatments for advanced disease, but a review of these data is beyond the scope of this paper.

Several new anti-oestrogens have been developed since tamoxifen, some with similar mechanisms of action to tamoxifen and some that are very different. First-generation SERMs, such as toremifene, droloxifene and idoxifene, are tamoxifen analogues based on the non-steroidal triphenylethylene structure. The structurally distinct second- and third-generation SERMs (raloxifene, arzoxifene, EM-800 and ERA-923) are also non-steroidal, but are 'fixed-ring' benzothiophene derivatives, yet appear to retain some oestrogen agonist activity. In contrast, fulvestrant, which has a steroidal structure closely resembling oestradiol, is a new ER antagonist that has no agonist activity. Fig. 1 shows the chemical structures of oestradiol, fulvestrant, tamoxifen and raloxifene. Anti-oestrogens are generally compared on the basis of their activity in tamoxifen-resistant disease, their ability to delay the development of resistance and their side-effect profiles.

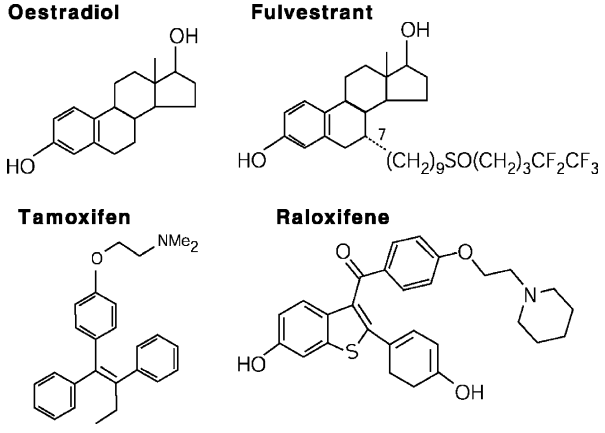

Fig. 1. Chemical structures of oestradiol, fulvestrant, tamoxifen and raloxifene.

3. Activity *versus* tamoxifen and in tamoxifen-resistant disease

3.1. SERMs

Several studies have confirmed that toremifene is cross-resistant with tamoxifen in advanced disease [9–11]. Both these agents display similar efficacy and tolerability in the advanced [12,13] and adjuvant settings [14]. Efficacy results for the structurally related, droloxifene [15–17] and idoxifene [18,19], have both been disappointing when either compared directly with tamoxifen or when used in tamoxifen-resistant disease; the development of these agents has now ceased.

The second-generation, 'fixed ring' SERM arzoxifene has also shown poor efficacy in tamoxifen-resistant disease [20]. Furthermore, a randomised Phase III trial of arzoxifene *versus* tamoxifen was terminated early because of a lack of efficacy (Buzdar A, data not shown). Raloxifene also shows low efficacy in tamoxifen-resistant disease [21], but has shown promise in breast cancer prevention [22,23] and is currently being tested in this setting in the STAR (Study of Tamoxifen and Raloxifene) trial [24]. ERA-923 is a second-generation SERM that is currently in development for the treatment of tamoxifen-refractory metastatic breast cancer, but no efficacy data for this agent are available to date. In summary, the SERMs as a group have thus far shown no superiority over tamoxifen as first-line advanced breast cancer treatments and minimal activity in tamoxifen-resistant disease.

3.2. High-dose oestrogens

Prior to the introduction of tamoxifen, high-dose oestrogens – such as diethylstilboestrol (DES) or ethinyl oestradiol – were generally considered the endocrine treatment of choice for postmenopausal women with breast cancer [25]. Subsequently, the use of oestrogens declined, but recent trial data have shown these drugs to have similar efficacy to tamoxifen [26] and to produce responses, even in those who have received extensive prior endocrine therapy [27]. However, the use of these agents is limited by their toxicity profile.

4. Fulvestrant – a novel oestrogen antagonist that downregulates cellular levels of ER

4.1. Biological effects

Fulvestrant blocks the trophic actions of oestrogen without exerting any partial agonist effects. Fulvestrant entered clinical development after preclinical studies suggested it was active in tamoxifen-resistant breast

cancer [28–30]. Fulvestrant acts by competing with oestradiol for binding to the ER and has a higher affinity for the ER than tamoxifen [31]. Fulvestrant downregulates expression of ER and decreased activity of the ER pathway results in reduced expression of the PgR and reduced proliferative and cell turnover indices both *in vitro* [32–35] and in the clinical setting [36,37].

In the presence of fulvestrant, ER is rapidly depleted, producing a loss of functional response to oestrogens after relatively short periods of time in *in vitro* studies. This is in contrast with the increases in ER levels seen on either oestrogen withdrawal or tamoxifen treatment [32]. The effects of three different fulvestrant doses and one dose of tamoxifen on cellular ER, PgR and Ki67 levels were investigated in a study of postmenopausal women with primary breast cancer. Patients received either a single intramuscular (i.m.) injection of fulvestrant 50, 125 or 250 mg, or oral tamoxifen 20 mg, daily for 14–21 days, prior to surgery of curative intent. Fig. 2 demonstrates the dose-dependent reductions in ER and PgR levels with fulvestrant treatment. Reductions in ER levels were statistically significant for all fulvestrant doses compared with placebo and for the 250 mg dose compared with tamoxifen. There were statistically significant reductions in PgR levels with fulvestrant 125 and 250 mg compared with placebo. In contrast, tamoxifen treatment produced significant increases in PgR levels compared with placebo, probably as a result of its oestrogen agonist activity. All doses of fulvestrant significantly reduced the Ki67 labelling index, but there were no significant differences compared with tamoxifen [36].

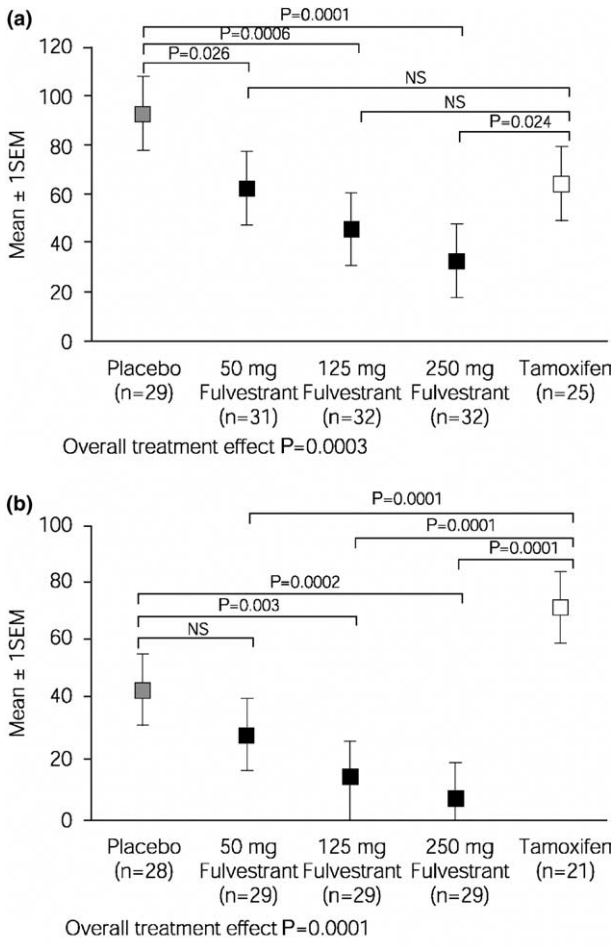

Fig. 2. Post-treatment mean H-scores for cellular: (a) oestrogen receptor (ER) and (b) progesterone receptor (PgR) levels. Figure reproduced with the permission of Cancer Research [36]. SEM, standard error of the mean; NS, non-significant.

4.2. Clinical efficacy

4.2.1. Fulvestrant versus anastrozole

Two large Phase III trials (Trial 0021: North American; Trial 0020: Rest of World [Europe, South Africa, Australia]) have compared the efficacy and tolerability of fulvestrant with anastrozole, in postmenopausal women with advanced breast cancer who had progressed on prior endocrine treatment (mainly tamoxifen). Patients were randomised to receive either fulvestrant 250 mg, by monthly i.m. injection or a daily oral dose of anastrozole 1 mg and continued treatment until disease progression or withdrawal.

In the North American trial, 400 patients received double-blind, randomised treatment with either fulvestrant (as 2×2.5 ml i.m. injections) ($n = 206$) or oral anastrozole ($n = 194$) and were followed for a median of 16.8 months. Fulvestrant was found to be as effective as anastrozole in terms of time to progression (TTP) (Hazard Ratio (HR): 0.92; 95% Confidence Interval (CI) 0.74–1.14; $P = 0.43$); median TTP was 5.4 months with fulvestrant and 3.4 months with anastrozole. Objective response (OR) rates were 17.5% for both treatments and clinical benefit (complete response (CR) + partial response (PR) + stable disease (SD) $\geqslant$ 24 weeks; CB) rates were 42.2% and 36.1% for fulvestrant and anastrozole, respectively. Median duration of response (DOR; from randomisation to progression) was 19.0 months for fulvestrant compared with 10.8 months for anastrozole. An analysis using all randomised patients, defined for responders as the time from onset of response to disease progression and for non-responders as zero, showed that mean DOR was significantly greater for fulvestrant compared with anastrozole; the ratio of average response durations being 1.35 (95% CI 1.10–1.67; $P < 0.01$) [38].

In the Rest of World (open) trial, 451 patients were randomised to receive either fulvestrant as a single 5 ml i.m. injection ($n = 222$) or anastrozole orally ($n = 229$) and were followed for a median of 14.4 months. Again, fulvestrant was shown to be at least as effective as anastrozole in terms of TTP (HR: 0.98; 95% CI 0.80–1.21; $P = 0.84$); median TTP was 5.5

months for fulvestrant and 5.1 months for anastrozole. OR rates were 20.7% for fulvestrant and 15.7% for anastrozole (odds ratio: 1.38; 95% CI 0.84–2.29; $P = 0.20$). CB rates were 44.6% for fulvestrant and 45.0% for anastrozole and the median DOR was 15.0 months and 14.5 months for fulvestrant and anastrozole, respectively. In addition, mean DOR using all randomised patients was significantly greater for fulvestrant compared with anastrozole, the ratio of average response durations being 1.27 (95% CI 1.05–1.55; $P = 0.01$) [38].

The two Phase III trials were prospectively designed to be evaluated both individually and using combined data. A combined analysis of all patients included in both second-line Phase III trials demonstrated a significant 30% increase in mean DOR in patients treated with fulvestrant (ratio of average response durations: 1.30; 95% CI 1.13–1.50; $P < 0.01$; Fig. 3) [40]. In addition to confirming the efficacy of fulvestrant that was observed in the individual trials, retrospective analyses of these combined data also showed fulvestrant had similar efficacy (in terms of OR rate, CB rate and DOR) to anastrozole in the subgroup of patients with visceral metastases. The median DOR in patients with visceral metastases was 17.5 months in the fulvestrant group compared with 11.7 months in the anastrozole group. Notably, in the subgroup of patients with visceral metastases only, seven of 69 (10%) fulvestrant-treated patients achieved a CR, compared with one of 86 (1%) anastrozole-treated patients [41].

The data from these two trials reiterate that fulvestrant is a novel agent with levels of activity in tamoxifen-resistant disease that distinguish it from SERMs and other anti-oestrogens. Furthermore, fulvestrant was at least as effective as anastrozole in this setting. In addition, retrospective analysis evaluating combined questionnaire data from the two trials showed that patients can retain sensitivity to other endocrine agents (anastrozole, letrozole, and megestrol acetate) after receiving second-line fulvestrant (Table 1) [42].

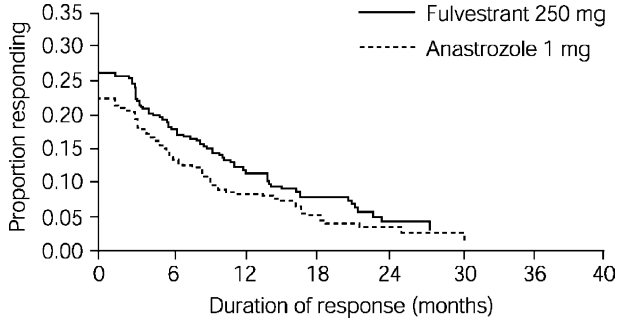

Fig. 3. Kaplan–Meier estimates for duration of response from onset of response to disease progression (combined analysis of all randomised patients included in Phase III trials). Copyright © 2003 American Cancer Society. Reprinted by permission of Wiley - Liss, Inc., a subsidrary of John Wiley & Sons, Inc. [40].

Table 1
Response to subsequent therapy in patients who derived CB from fulvestrant

	Number of patients				
	CR	PR	SD ⩾ 24 weeks	PD	Total
Patients who derived CB from first-line fulvestrant					
Anastrozole	1	0	8	7	16
Letrozole	0	1	0	4	5
Fadrozole	0	0	1	0	1
Tamoxifen	0	1	7	2	10
Megestrol acetate	0	0	1	0	1
Medroxyprogesterone acetate	0	0	0	2	2
Patients who derived CB from second-line fulvestrant					
Anastrozole	0	1	13	23	37
Letrozole	0	2	3	3	8
Formestane	0	0	0	1	1
Megestrol acetate	0	1	5	2	8

Table adapted from [44] and [42], with the permission of Breast Cancer Research and Treatment.
CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; CB, Clinical benefit.

4.2.2. *Fulvestrant versus tamoxifen*

Fulvestrant and tamoxifen have been compared as first-line treatments in a trial including postmenopausal women with advanced breast cancer. Approximately, 20–25% of patients in this trial had previously received adjuvant tamoxifen, but no patients received prior endocrine therapy for advanced disease. In this study, the median TTP was 6.8 months in the fulvestrant group and 8.3 months in the tamoxifen group. The between-treatment difference was non-significant (HR: 1.18; 95% CI 0.98–1.44; $P = 0.088$), but the upper limit of the 95% CI (1.44) did not satisfy the pre-defined criterion for non-inferiority ($\leqslant 1.25$) of fulvestrant compared with tamoxifen. OR rates for fulvestrant and tamoxifen were similar (31.6% *versus* 33.9%; $P = 0.45$), but more tamoxifen-treated patients overall achieved CB (62.0% *versus* 54.3%; $P = 0.03$) [43]. Median DOR (from randomisation to progression) was 17.3 and 19.8 months for fulvestrant and tamoxifen, respectively [43]. In the prospectively defined subgroup of patients with ER-positive and/or PgR-positive tumours, median TTP was similar for the fulvestrant and tamoxifen treatment groups (8.2 months *versus* 8.3 months; HR: 1.10; 95% CI 0.89–1.36; $P = 0.39$) [43].

Subsequent exploratory analyses of response by hormone receptor status showed that in the subgroup of patients with tumours expressing both ER and PgR 44.3% of fulvestrant-treated patients and 29.8% of patients treated with tamoxifen experienced an OR ($P = 0.02$) [43]. However, the authors note that these data were retrospectively derived and therefore should be interpreted with caution in terms of their clinical significance. Further confirmatory data are required. In addition, patients who responded to first-line treatment with

fulvestrant may retain sensitivity to subsequent endocrine therapy with a variety of agents, including anastrozole, letrozole, fadrozole, tamoxifen, and megestrol acetate (Table 1) [44]. This is similar to the findings noted above where tumours appeared to retain sensitivity to other endocrine agents following second-line treatment with fulvestrant [42]. It therefore appears that the use of fulvestrant does not *per se* lead to end-stage hormone insensitivity.

4.3. Tolerability

In the second-line trials, both fulvestrant and anastrozole were well tolerated, with few patients in either group withdrawing due to treatment-related adverse events (0.9% and 1.2% of the fulvestrant- and anastrozole-treated patients, respectively). Overall, the incidence and severity of events (generally mild to moderate) were similar between groups; the most common events in both groups included hot flushes, nausea, asthenia, pain, headache and pharyngitis. The incidence of events considered important with endocrine therapy such as weight gain, thromboembolic events and vaginitis was low for both fulvestrant and anastrozole [38,39].

The use of placebo injections in the North American trial indicated that fulvestrant was well tolerated locally and that injection-site reactions were related to the injection itself, as 27% of patients receiving fulvestrant compared with 23% of those receiving placebo reported injection-site reactions [38]. Overall, 86 fulvestrant courses (4.6%) of the total 1879 and 71 placebo courses (4.4%) of the total 1624 resulted in an injection-site reaction. This is supported by the clinical experience of physicians administering the 2×2.5 ml fulvestrant regimen in the US. Here, nursing guidelines have previously suggested that, for adults, i.m. injections into large muscles such as the gluteus medias, should not usually exceed 4 ml [45], therefore in the trial it was decided to use 2×2.5 ml i.m. injections, one into each buttock, rather than a single 5 ml injection [38]. The pharmacokinetics of these two regimens have previously been shown to be similar [46]. Moreover, since the 2.5 ml injections were so well tolerated, most US institutions now prefer to administer fulvestrant as a single 5 ml i.m. injection, thereby reducing the number of injections given to the patient (AstraZeneca, data on file).

In the fulvestrant *versus* tamoxifen comparative study, both treatments were well tolerated with no statistically significant differences in the incidence of prospectively defined adverse events of gastrointestinal disturbances, hot flushes, vaginitis and thromboembolic disease. However, the incidence of hot flushes was lower in the fulvestrant group than in the tamoxifen group and the difference approached statistical significance (17.7% *versus* 24.7%; $P = 0.0501$) [43].

5. Fulvestrant – the US experience

In April 2002, the US Food and Drug Administration (FDA) granted approval for fulvestrant to be used for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following anti-oestrogen therapy. The use of fulvestrant as second-line therapy is increasing, although the drug continues to be used in patients who have progressed on both tamoxifen and an AI. Data from the two Phase III studies of fulvestrant *versus* anastrozole suggest that fulvestrant is as effective as an AI in the second-line setting and that DOR may, in fact, be longer with fulvestrant treatment [38,39].

In the US, there appears to be a general underutilisation of hormonal therapy and a lack of differentiation between fulvestrant and other hormonal agents such as anastrozole. At several oncology meetings in the US, surveys of treatment practice amongst US oncologists suggest that US physicians often favour chemotherapy in situations where European clinicians prefer further endocrine treatment. Furthermore, US physicians may utilise endocrine treatment for a shorter duration and switch to chemotherapy earlier than their European counterparts (Jones SE, data not shown).

The personal experiences of the US physicians involved in the US Phase III fulvestrant *versus* anastrozole trial are in agreement with the formal DOR analysis, which suggest that, on average, fulvestrant-treated patients respond for approximately 30% longer than those treated with anastrozole [40]. One investigator had 27 patients included in the Phase III US trial, of these, five have had responses of >3 years (two for >4 years), four of these patients have now relapsed and have been unblinded and all had been receiving fulvestrant and one is currently continuing double-blind treatment (Jones SE, data not shown). A second investigator had 16 patients entered in the same trial; four of these patients (25%) had CB for 20–44 months three of whom were found to be receiving fulvestrant after unblinding (Come SE, Personal Communication) (Table 2). This emphasises the fact that there appears to be a population of patients who have an extremely long DOR with fulvestrant. Furthermore, personal experiences from these physicians have shown that parenteral dosing can also be beneficial over oral dosing for some patients, particularly those demonstrating poor compliance with oral therapies.

6. Sequencing of endocrine treatments

Because of the toxicity associated with chemotherapy, it would be advantageous in appropriate patients to extend the endocrine treatment window, thus deferring the initiation of more toxic treatments that are associated with acute and more severe side effects. Endocrine treat-

Table 2
Case studies from the US phase III fulvestrant *versus* anastrozole trial (Come SE, Personal Communication)

Patient characteristics	Efficacy results
Case study 1	
• 55 years old	• SD of 20 months duration on fulvestrant
• ER-positive infiltrating lobular carcinoma	• SD of 7 months duration on anastrozole (after code-break)
• Developed metastases to the colon during adjuvant tamoxifen treatment	
Case study 2	
• 59 years old	• SD of 39 months duration on fulvestrant
• ER-positive/PgR-positive tumour	• SD of 7 months duration on anastrozole (after code-break)
• Metastases to liver, bone, skin, and lymph nodes	
Case study 3	
• 64 years old	• CR of 44 months on fulvestrant[a]
• ER-positive tumour	• Still receiving fulvestrant outside of trial setting and still in CR (currently of 55 months duration)
• Skin metastases (following first-line tamoxifen treatment)	

ER, oestrogen receptor; PgR, progesterone receptor; SD, stable disease; CR, complete response.
[a] Patient withdrew from the trial whilst experiencing a CR (at that time of 44 months duration) to receive off-study treatment with fulvestrant closer to home.

ment should generally continue as long as the patient remains hormone sensitive (i.e., achieving CB with hormone treatment) and when the patient becomes hormone resistant, chemotherapy treatment should then be initiated. For the past 20 years, the most commonly used first-line or adjuvant endocrine treatment for advanced breast cancer has been tamoxifen. However, the non-steroidal AIs are now used routinely in the advanced setting and are also starting to be used as adjuvant treatment following the recently reported results from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial [47].

Two schema of treatment options following adjuvant or first-line tamoxifen treatment (Fig. 4(a)) or adjuvant

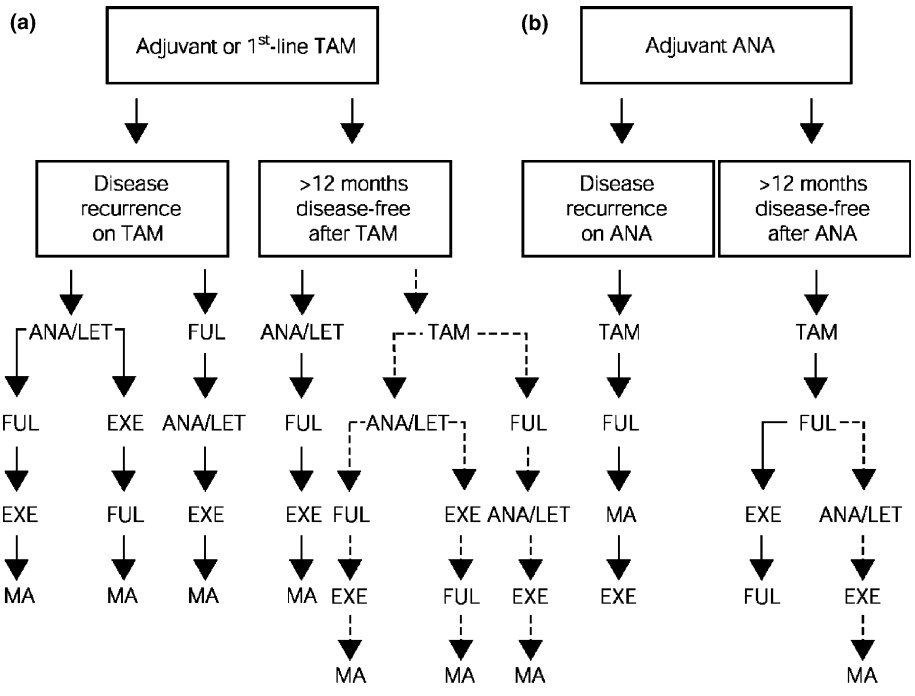

Fig. 4. Treatment options flow charts for patients previously treated with: (a) adjuvant or first-line tamoxifen; (b) adjuvant anastrozole.

anastrozole treatment (Fig. 4(b)) are proposed. These suggestions have been based on data from randomised clinical trials where available, or otherwise, on non-randomised data or the authors' personal experiences.

6.1. Treatment options following adjuvant or first-line tamoxifen

If a patient experiences disease recurrence on adjuvant or progressive disease on first-line tamoxifen treatment (Fig. 4(a)), there is sufficient evidence to show that fulvestrant is comparable to anastrozole in these patients [38,39], and the longer DOR with fulvestrant treatment may suggest an advantage for fulvestrant in this setting [40]. At the current time, despite these data, the wealth of clinical experience with AIs may mean that these agents could be the most comfortable treatment choice for many physicians.

There is evidence to suggest that patients receiving fulvestrant may retain sensitivity to tamoxifen and non-steroidal AIs [42,44]. Fulvestrant or exemestane (a steroidal AI) could be considered following second-line treatment with a non-steroidal AI. Preliminary data from a small Phase II study suggests that fulvestrant is effective in this setting [48], although more data are available to support the reverse sequence (fulvestrant followed by an AI). High-dose oestrogens could also be used following AI failure [27]. However, the toxicities of this type of treatment may limit the use of this option. Data from a large Phase III trial is needed to clarify the optimal choice of sequence at this point.

Exemestane has shown activity in women with advanced breast cancer previously treated with non-steroidal AIs such as aminoglutethimide, anastrozole and letrozole [49]. Exemestane has shown superior efficacy and tolerability over megestrol acetate, after tamoxifen failure, in postmenopausal women with advanced breast cancer [50], and therefore this agent is now chosen ahead of megestrol acetate in most situations. Further data regarding the sequencing of AIs was presented in 2002 at the annual meeting of the American Society of Clinical Oncology. Bertelli and colleagues [51] investigated whether patients who had previously received exemestane could still benefit from treatment with anastrozole or letrozole after exemestane failure and *vice versa*. One PR, two SD and one disease progression (PD) were observed amongst the first five patients receiving non-steroidal AIs after exemestane. Responses to exemestane after treatment with non-steroidal AIs were similar to those observed in previous studies, being 3 PR, 3 SD, and 4 PD in the first 17 evaluable patients. Although preliminary, these data suggest that there is some evidence for a lack of cross-resistance between steroidal and non-steroidal AIs [51]. The Evaluation of Faslodex (fulvestrant) *versus* Exemestane Clinical Trial (EFECT) will compare the efficacy of fulvestrant and exemestane in postmenopausal women with advanced breast cancer who have progressed after prior non-steroidal AI treatment. Data from this trial will help to address this part of the algorithm.

If a patient has a disease-free interval >12 months following adjuvant or first-line tamoxifen, the choice of subsequent treatment is slightly different. With no evidence indicating superiority of fulvestrant over tamoxifen in the first-line setting, a more appropriate treatment choice may be a non-steroidal AI [4–7]. A second possibility, after a disease-free interval of >12 months would be to rechallenge with tamoxifen and follow a similar schedule to that shown previously. However, a patient may be uncomfortable receiving the same treatment and may want to receive a new agent, in which case an AI would be recommended.

6.2. Treatment options following adjuvant anastrozole

Anastrozole is the only non-steroidal AI to have proven efficacy for adjuvant treatment and provides an alternative to tamoxifen in this setting. Treatment options following the use of adjuvant anastrozole are presented in Fig. 4(b). There is a lack of randomised controlled trial data to support an optimal sequence following either failure on adjuvant anastrozole or a disease-free interval of >12 months. However, it would seem sensible in both situations to try an agent with a different mechanism of action such as an anti-oestrogen, although following a disease-free interval of >12 months, rechallenge with anastrozole may also be a possibility. However, these authors suggest that fulvestrant or tamoxifen would both be the valid choices in this setting, but because of the wealth of clinical experience with tamoxifen over the last 25 years, they would recommend tamoxifen after adjuvant anastrozole treatment. A further reason for the use of tamoxifen followed by fulvestrant rather than the reverse sequence is that data from the two large Phase III fulvestrant *versus* anastrozole trials show that this particular sequence works well [38,39]. While the reverse sequence has also been shown to be effective the volume of data is less extensive.

The sequence of treatment choices following fulvestrant are similar to those presented earlier; the only difference is that following disease recurrence on adjuvant anastrozole, there is a rationale for the use of megestrol acetate ahead of exemestane, due to its different mechanism of action. Another possibility is the use of high-dose oestrogens [27]. Overall however, there is a lack of randomised trial data to clearly define an optimum sequence of endocrine therapies and until this becomes available, clinical experience should shape future use.

7. Fulvestrant – future developments

7.1. Possibilities for further enhancing the efficacy of fulvestrant

Dose-dependent reductions in ER levels have been reported previously both in preclinical studies and in fulvestrant-treated patients [33,36]. *In vitro* studies in human breast cancer cell lines (MCF-7) show that incubation with fulvestrant results in a rapid and dramatic reduction in ER protein levels, leading to an almost total loss of ER [33]. Although fulvestrant 250 mg has already been shown to be as effective as anastrozole, the level of ER downregulation achieved in a neoadjuvant trial using the long-acting fulvestrant formulation [36] has not yet matched that seen in some of the early preclinical studies [32,33] or with the short-acting formulation [52]. However, as the duration of treatment in the Robertson study was very short (one single injection 14–21 days prior to surgery), it is possible that with longer treatment, more effective ER downregulation may be achieved [36].

The possibility of further downregulating ER in patients receiving fulvestrant was demonstrated in a study where postmenopausal women with primary breast cancer received a daily i.m injection of either 6 mg ($n = 37$) or 18 mg ($n = 21$) of a short-acting fulvestrant formulation for 7 days prior to surgery. Significant reductions in the median ER indices of ER-positive tumours were evident at both the 6 and 18 mg dose levels, decreasing from 0.60 to 0.06 in the 6 mg group ($P < 0.05$) and from 0.73 to 0.01 in the 18 mg group ($P < 0.01$) [52]. This compares with the approximate 60% downregulation of ER achieved using the clinical formulation [36].

As ER downregulation is a dose-dependent process it is possible that further reductions in ER levels may be achieved more rapidly and effectively with the use of more frequent dosing, higher fulvestrant doses or a loading dose. Further evidence for a relationship between fulvestrant dose and clinical efficacy was gained from the second-line Phase III trials. These trials were originally designed to compare two doses of fulvestrant (125 and 250 mg per month) with a 1 mg/day oral dose of anastrozole. However, an interim analysis was performed on the first 30 patients in the fulvestrant 125 mg arm, and failed to demonstrate sufficient evidence of clinical activity with no ORs after 3 months and so recruitment to this arm ceased. The protocol was amended to compare fulvestrant 250 mg/month with anastrozole 1 mg/day and this dose was found to be at least as effective as anastrozole in terms of OR rate [38,39].

When given by monthly 250 mg i.m. injection, in the manner currently shown to produce treatment responses, fulvestrant plasma concentration profiles reach steady-state after 3–6 doses [46]. However, the use of a loading-dose regimen may allow steady-state levels of fulvestrant to be achieved more rapidly. Such an approach may not impact on the long-term efficacy of the drug, but may allow early responses to be identified. It is possible to model the effects of the addition of a loading regimen on the attainment of steady-state fulvestrant levels (Fig. 5). Here, an initial dose of 500 mg fulvestrant is given on day 0, followed by 250 mg fulvestrant on day 14. This is followed 14 days later by the standard fulvestrant 250 mg monthly dose. The model demonstrates that steady-state is achieved between days 28–56 (Fig. 5). The use of a fulvestrant loading dose regimen will be investigated in several of the new fulvestrant clinical trials mentioned below.

As both the 1×5 ml and 2×2.5 ml fulvestrant 250 mg regimens are well tolerated, there is further potential to increase overall exposure to the drug and to achieve a more complete downregulation of ER with minimal risk of an additional adverse event burden. This could be achieved by administering either 2×5 ml monthly injections or by increasing the frequency of dosing, possibly with the use of a bi-weekly schedule.

7.2. New clinical trials

Several new trials comparing fulvestrant with other endocrine treatments and in combination with other agents are about to be initiated and are summarised below.

7.2.1. Fulvestrant versus exemestane

The trial EFECT aims to compare the efficacy of fulvestrant and exemestane in postmenopausal women with hormone receptor-positive advanced breast cancer who have progressed after prior anastrozole treatment. This study will utilise a loading dose regimen for fulvestrant. The study will recruit 660 patients across the US, Canada and Europe and the primary efficacy endpoint will be TTP.

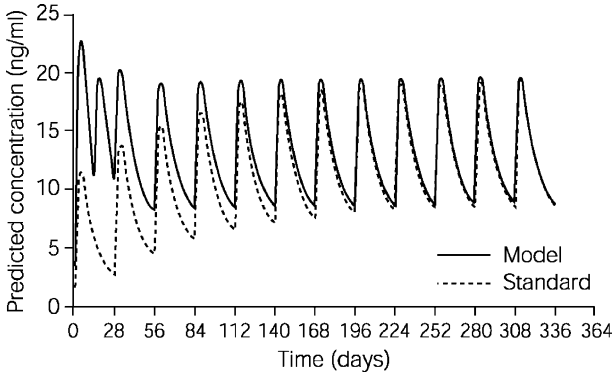

Fig. 5. Loading-dose regimen pharmacokinetic model: fulvestrant 500 mg on day 0, 250 mg on days 14 and 28 and then 250 mg every 4 weeks compared with the standard 250 mg every 4 weeks regimen.

7.2.2. Fulvestrant plus anastrozole

Theoretically, the combination of fulvestrant and anastrozole could result in an additive antitumour effect. As a result, this combination is soon to be investigated in several new clinical trials, one of which will be run cooperatively by the Eastern Cooperative Oncology Group (ECOG) and the South-West Oncology Group (SWOG). Another efficacy trial assessing this combination is being conducted in the second-line treatment of patients failing on tamoxifen. A neoadjuvant marker study comparing the level of ER downregulation observed with anastrozole and fulvestrant alone and that seen with combination treatment is also planned. Although the ATAC trial did not show any benefit from combining anastrozole and tamoxifen compared with tamoxifen or anastrozole alone [47], this may be due to the partial agonist effect of tamoxifen. Since fulvestrant has no agonist activity, it is hoped that any benefits of simultaneously impeding both receptor activation and oestrogen synthesis may be demonstrated with the fulvestrant plus anastrozole combination.

The SOFEA (Study of Faslodex *versus* Exemestane with/without Arimidex) trial will compare the efficacy of fulvestrant alone with fulvestrant plus anastrozole in postmenopausal women with locally advanced or metastatic breast cancer who have progressed on anastrozole. This study will also utilise a fulvestrant loading-dose regimen and will include a control reference arm in which patients will receive exemestane alone.

7.2.3. Fulvestrant plus gefitinib ('Iressa', ZD1839)

Cross-talk between ER and epidermal growth factor (EGF)/human EGF receptor 2 (HER2) receptor pathway is believed to be associated with endocrine resistance [53]. Tamoxifen is linked to increased cellular signalling via the EGF receptor (EGFR) and with sensitivity to EGFR inhibitors. Combining tamoxifen with gefitinib ('Iressa') delays the development of endocrine resistance in breast cancer models [54]. It is hoped that the combination of fulvestrant, (which disrupts ER signalling) with gefitinib (which disrupts EGFR signalling) may potentially prevent receptor cross-talk, and thus help prevent or overcome the development of resistance. The combinations of fulvestrant plus gefitinib and anastrozole plus gefitinib will be evaluated in a randomised Phase II ECOG trial in the near future (Come SE, data not shown).

8. Conclusions

Fulvestrant is a novel agent with a unique mechanism of action, distinct from other anti-oestrogens and SERMs. Fulvestrant is at least as effective as the most widely used AI, anastrozole, in the second-line treatment of postmenopausal women with advanced breast cancer and may have advantages in terms of efficacy in patients with visceral metastases and in the duration of response. However, there may be potential for a further enhancement (e.g., with the use of a loading-dose regimen). Fulvestrant is not cross-resistant with other endocrine agents used for the treatment of hormone receptor-positive metastatic breast cancer and thus it may be necessary to rethink the conventional sequencing of endocrine treatments. However, new trials are needed to more clearly define the optimal sequence of endocrine therapies. Because of its different mode of action and good tolerability profile, fulvestrant is an ideal agent for combination treatment with other endocrine treatments and/or novel agents. New trials are underway to investigate fulvestrant in combination with anastrozole and gefitinib.

Conflict of interest statement

This manuscript arose from a meeting that was supported by an unrestricted educational grant from AstraZeneca. In addition, the following authors have other potential financial conflicts of interest: John F.R. Robertson has performed contract work and received speaking honoraria from AstraZeneca and Novartis. Steven E. Come has received research support and speaking honoraria from AstraZeneca, Aventis and Novartis. He also provided expert testimony for Genentech. Stephen E. Jones has acted as a consultant for AstraZeneca and has received speaking honoraria from this company. Louk Beex has acted as a consultant for AstraZeneca and has received travel grants from this company. Manfred Kaufmann has received travel grants, speaking honoraria and research support from Pfizer and AstraZeneca. Andreas Makris has received honoraria and travel grants from AstraZeneca. Kurt Possinger has acted as a consultant to Novartis and AstraZeneca and has received travel grants from both companies. Lars-Erik Rutqvist is a principal investigator on a clinical trial sponsored by AstraZeneca.

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