Advanced disease – the optimal sequential treatment strategy

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Introduction

Treatments for advanced breast cancer (ABC) are essentially palliative and so in addition to efficacy, issues of tolerability, quality of life and patient preference are important considerations when evaluating available options [1]. Which treatment is chosen also depends on various patient and disease characteristics including: the patient' s age/menopausal status, the hormone receptor and human epidermal growth factor receptor 2 (HER2) status of the tumour, as well as any previous therapies for breast cancer. In patients with hormone receptor (estrogen receptor [ER] and/or progesterone receptor)-positive disease, endocrine therapy is usually the treatment of choice as it has similar efficacy to cytotoxic chemotherapy, but is better tolerated [2].

In general terms, endocrine therapies work in one of two different ways. The first mechanism is to block estrogen production, which in premenopausal women could be via ovarian ablation (oophorectomy, ovarian irradiation or using a luteinising hormone-releasing hormone analogue [LHRHa]). In postmenopausal women, aromatase inhibitors (AIs) can be used to block the peripheral conversion of androgens to estrogens via the aromatase enzyme. The second mechanism is to block estrogen action at the ER using antiestrogens such as tamoxifen, other selective estrogen receptor modulators (SERMs) or new ER antagonists like fulvestrant. Antiestrogens have the potential to be used in both pre- and postmenopausal patients with breast cancer.

Endocrine treatment options for postmenopausal women with ABC

Antiestrogens

Tamoxifen and other SERMs

Although it has proven survival benefits, tamoxifen is also associated with an increased risk of endometrial cancer, thromboembolic disease and tumour ' flare' primarily due to its estrogen agonist effects [3–5]. Furthermore, most tumours eventually develop resistance to tamoxifen, resulting in the need for further treatment options [6]. For these reasons, investigators have tried to improve on the efficacy and tolerability of tamoxifen with the development of newer first- and second-generation SERMs, but with limited success. First-generation SERMs such as toremifene, droloxifene and idoxifene were found to be cross-resistant with tamoxifen and to have agonist effects on the uterus. Clinical data for second-generation SERMs such as raloxifene and arzoxifene were also disappointing showing that they offered no benefits over tamoxifen and were ineffective in tamoxifen-resistant disease [7].

Fulvestrant

Fulvestrant is a new ' pure' antiestrogen – an ER antagonist with no agonist effects. It has a novel mode of action distinct from other endocrine agents; it binds, blocks and degrades the ER. Unlike SERMs, fulvestrant is effective in tamoxifen-resistant disease [8].

Fulvestrant (250 mg via once-monthly intramuscular injection) has been compared with anastrozole (1 mg/day, orally) in two phase III trials in 851 postmenopausal women with ABC who had progressed or relapsed on prior tamoxifen therapy [9,10]. A prospective, combined analysis of the data from these two trials showed that, at a median follow-up of 15.1 months, the median times to progression [TTP] were 5.5 months versus 4.1 months, and overall response rates were 19.2% versus 16.5% for fulvestrant and anastrozole, respectively. The median durations of response were 16.7 months for fulvestrant and 13.7 months for anastrozole [8]. At an extended median follow-up of 27.2 months, median overall survival was not significantly different in the two treatment groups (27.4 months versus 27.7 months, respectively; HR 0.98; 95%CI: 0.84, 1.15; $p = 0.81$) [11]. These data demonstrate that fulvestrant is at least as effective as anastrozole in the second-line treatment of postmenopausal women with ABC who have progressed or relapsed on/after antiestrogen therapy. Fulvestrant was also well tolerated both locally and

systemically and was associated with significantly fewer joint disorders (including arthralgia, arthrosis and arthritis) compared with anastrozole (5.4% versus 10.6%, respectively; $p < 0.004$) [8]. Based on these and other data, fulvestrant was licensed for the treatment of hormone receptor-positive ABC in postmenopausal women progressing or relapsing on prior antiestrogen therapy. Currently, fulvestrant is the only agent in its class to be approved for use in the clinic.

AIs

First- and second-generation AIs

First- and second-generation AIs such as aminoglutethimide and formestane showed efficacy following progression on tamoxifen but were relatively poorly tolerated [12–14]. Third-generation non-steroidal AIs such as anastrozole, letrozole and the steroidal AI exemestane have since been developed which suppress oestradiol levels more effectively and are better tolerated than earlier agents [15].

Third-generation AIs

Third-generation AIs have shown efficacy and tolerability benefits over tamoxifen in ABC and in the adjuvant setting. They include both nonsteroidal (anastrozole and letrozole) and steroidal (exemestane) agents.

Anastrozole. Anastrozole (1 mg/day) has been compared with tamoxifen (20 mg/day) as first-line therapy in two phase III, multicentre trials involving 1145 postmenopausal women with ABC [16,17]. A prospectively defined combined analysis of the data from these trials was performed after a median follow-up of 18.5 months and included 551 patients who received anastrozole and 510 who received tamoxifen. In the overall population, median TTP was 8.5 months for anastrozole treated patients versus 7.0 months for tamoxifen-treated patients ($p = 0.103$) and objective response rates were also similar (29.0% versus 27.1%, respectively). Clinical benefit rates were 57.1% for anastrozole and 52% for tamoxifen ($p = 0.1129$). For patients with hormone receptor-positive tumours (approximately 60% of patients), median TTP was significantly longer for anastrozole compared with tamoxifen (10.7 months versus 6.4 months, respectively; $p = 0.022$). Anastrozole was also associated with significantly fewer venous thromboembolic events than tamoxifen [18].

At an extended median follow-up of 43.7 months, 56.0% of patients in the anastrozole group and 56.1% of patients in the tamoxifen group had died and median overall survival was similar between treatments. Both agents remained well tolerated, with fewer reports of vaginal bleeding (1.0% versus 2.5%) and thromboembolic events (5.3% versus 9.0%) in the anastrozole group compared with those receiving tamoxifen. Although no improvement in overall survival was observed, the favourable profile of anastrozole with respect to efficacy (TTP) and tolerability supported the use of anastrozole ahead of tamoxifen as a first-line therapy choice in postmenopausal women with ABC.

Letrozole. A multicentre, double-blind, phase III trial has compared letrozole (2.5 mg/day) with tamoxifen (20 mg/day) as first-line treatments in 907 postmenopausal women with ABC [19]. Median TTP was significantly longer for patients receiving letrozole than for those receiving tamoxifen (41 versus 26 weeks, respectively) and letrozole was also superior in median time to treatment failure (40 weeks versus 25 weeks, respectively; $p = 0.0001$). Significantly more letrozole-treated patients experienced objective responses compared with those treated with tamoxifen (30% versus 20%, respectively; $p = 0.0006$). These data were confirmed in a follow-up study that also reported survival data; median overall survival was not significantly different between treatments; 34 months for letrozole and 30 months for tamoxifen [20]. If appropriate, patients experiencing disease progression were permitted to crossover to the alternative treatment in this study. It was reported that patients who initially received letrozole had a longer overall duration of endocrine therapy compared with those initially receiving tamoxifen (median of 16 months versus 9 months, respectively).

Exemestane. A phase II study has compared exemestane (25 mg/day) with tamoxifen (20 mg/day) as first-line treatments for ABC in 120 postmenopausal women [21]. Mature data from this trial showed that although the median duration of response for exemestane was less than that for tamoxifen (16 months versus 22 months, respectively), the objective response rate was higher in the exemestane group (41% versus 17%, respectively). It was concluded that exemestane was well tolerated and active in the first-line treatment of ABC and, as a result, the study was extended into phase III. Here, exemestane was associated with a significantly longer progression-free survival compared with tamoxifen (10.9 versus 6.7 months, respectively) [22]. In the final analysis of this study, conducted at a median follow-up of 29 months, again, more objective responses were seen in patients receiving exemestane (46% versus 31%; $p = 0.05$), but progression-free and overall survival were not significantly different between groups [23]. Arthralgia and diarrhoea were more commen in patients receiving

exemestane, while oedema, constipation, hot flushes, sweating, vaginal bleeding, and vaginal discharge were all more common in those receiving tamoxifen.

Third-generation AIs as first-line treatments for postmenopausal women with ABC

These data demonstrate that the third-generation AIs have an improved efficacy and tolerability profile compared with tamoxifen and are therefore now the preferred standard first-line treatment for postmenopausal women with ABC. In recent years, trials in patients with early breast cancer have also supported the superiority of AIs and these agents are now also starting to be used in the adjuvant setting ahead of tamoxifen [24–26] and in sequence with tamoxifen [27–33]. This has resulted in a requirement for new first-line and second-line treatments for ABC, particularly for agents that are effective following progression on AIs.

Sequencing of treatments for postmenopausal women with ABC

The use of a sequential cascade of non-cross-resistant therapies is the norm in the endocrine treatment of postmenopausal ABC. The order in which treatments are given depends on which prior adjuvant or first-line treatments the patient has received and their responses to such agents as well as any history of thromboembolic disease. For postmenopausal patients with ABC, there are now two main sequencing scenarios. The first is for those who have progressed or relapsed on or after tamoxifen treatment (as adjuvant therapy or for ABC) and the second is for those who have progressed or relapsed on or after AI treatment (as adjuvant or for ABC). A third, less common situation would result from those women relapsing following a sequence of tamoxifen and an AI as adjuvant therapy.

Several agents including AIs and fulvestrant are effective following tamoxifen failure and if a patient still remains sensitive, tamoxifen may also be reused, although it may be better to use a new agent with a different mode of action. However, as tamoxifen is often no longer the first treatment received for breast cancer, an important question is what to use following progression on AIs (particularly the non-steroidal AIs – which are more commonly used as initial treatments).

Efficacy of tamoxifen following non-steroidal AI failure

Retrospective questionnaire data from the Tamoxifen or ' Arimidex' Randomized Group Efficacy and Tolerability (TARGET) trial have suggested that tamoxifen may be an effective option following anastrozole failure. Of the 119 postmenopausal women with ABC included in this trial, 49% gained clinical benefit with second-line tamoxifen treatment [34]. Clinical benefit rates have not been reported for patients receiving tamoxifen following progression on letrozole, but survival data from a crossover analysis of a phase III trial suggest that this sequence is less effective than the reverse. In this analysis, median overall survival (from date of crossover) was 19 months for patients crossing from letrozole to tamoxifen, compared with 31 months for patients crossing from tamoxifen to letrozole [20].

Efficacy of fulvestrant following non-steroidal AI failure

Evidence for the efficacy of fulvestrant following non-steroidal AI failure has come from two phase II clinical trials as well as from a more ' real-life' setting of a Compassionate Use Programme. Final results have recently been reported from a phase II Swiss Group for Clinical Cancer Research (SAKK) trial assessing the efficacy of fulvestrant in patients who have progressed with both tamoxifen and an AI [35]. Of the 67 patients included in Stratum A (those who progressed while on AI treatment after initially gaining clinical benefit), 19 (28%) experienced clinical benefit with fulvestrant. Similar results were observed in a phase II trial conducted by the North Central Cancer Treatment Group (NCCTG). Of the 21 patients who had only received prior treatment with an AI (56 patients received prior tamoxifen and an AI), 11 patients (52.3%) gained clinical benefit with fulvestrant [36].

Several centres have reported information on the use of fulvestrant in a Compassionate Use Programme in patients with ABC who had received various prior endocrine treatments including tamoxifen, steroidal and non-steroidal AIs and progestins. For example, in a Czech centre where patients received fulvestrant as second- to fifth-line endocrine treatment, a clinical benefit rate of 52% was observed [37]. Similar results have been reported from a centre in Austria, where patients received fulvestrant as first- to fourth-line endocrine treatment. Here, 50 of 88 patients (56%) who had previously received a non-steroidal AI for ABC experienced stable disease or an objective response with fulvestrant treatment [38]. In general, better responses appeared to be observed when fulvestrant was

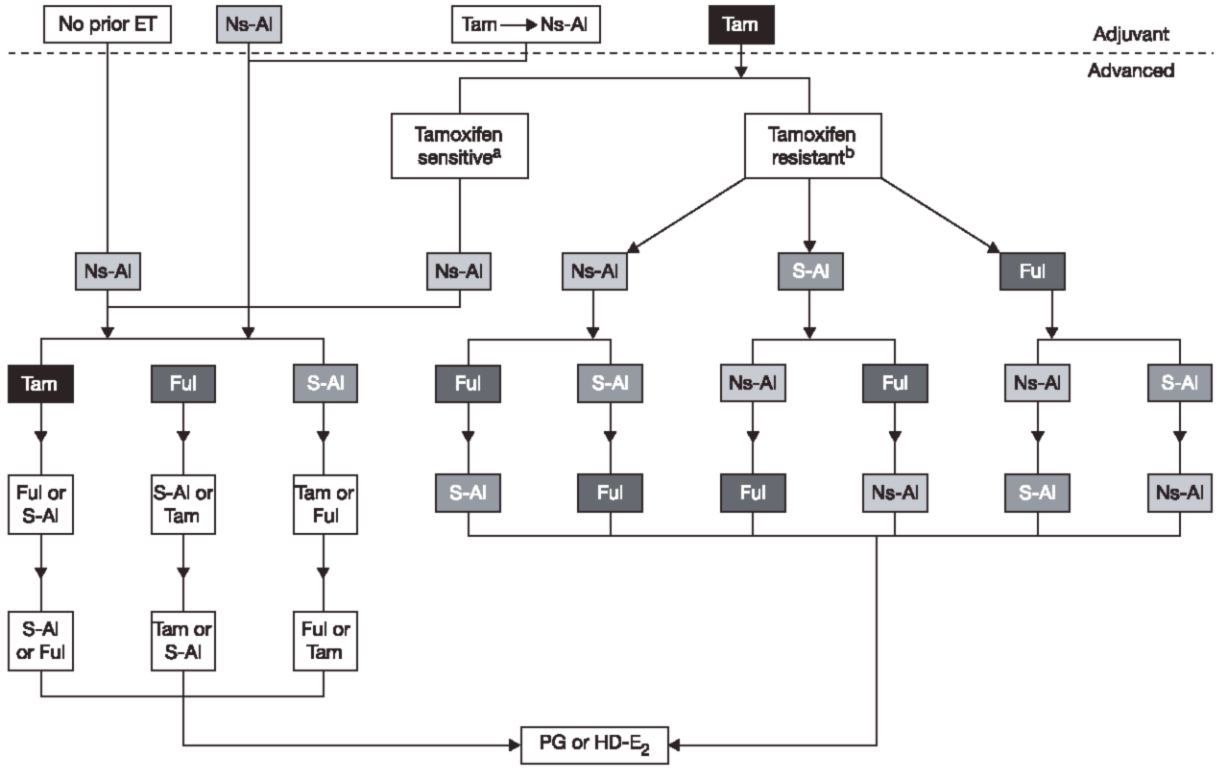

Fig. 1. Endocrine treatment sequencing in advanced breast cancer.

used earlier in the treatment sequence. Furthermore, patients progressing on fulvestrant remain sensitive to subsequent endocrine therapy [39], an important consideration when sequencing treatments.

Efficacy of the steroidal AI exemestane following non-steroidal AI failure

There are preliminary data to suggest a lack of cross-resistance between steroidal AIs and non-steroidal AIs and that steroidal AIs may be used following progression on non-steroidal AIs. In a phase II, open-label trial, 24% of patients gained clinical benefit with exemestane following treatment with the first-generation, non-steroidal AI aminoglutethimide or following third-generation AI treatment with anastrozole, letrozole or vorozole [40]. In further subset analyses, looking at patients who had received prior aminoglutethimide ($n = 136$) or prior third-generation AIs ($n = 105$), the clinical benefit rates were 27% and 20%, respectively, with subsequent exemestane treatment. A further report of a retrospective analysis of exemestane use in a ' real-life' setting also supports the activity of this agent following non-steroidal AI failure. Here, 37/96 patients (39%) receiving exemestane as second- to greater than fourth-line therapy experienced clinical benefit (89/96 [93%] of whom had received prior non-steroidal AIs) [41].

Based on these and other data, suggested schema showing the different treatment options following progression on tamoxifen, an AI, or tamoxifen and an AI, is shown in Fig. 1. Results from two ongoing phase III trials (Evaluation of Faslodex and Exemestane Clinical Trial [EFECT] and Study Of Faslodex, Exemestane and Arimidex (SOFEA) comparing fulvestrant and exemestane in patients progressing on a non-steroidal AI are awaited with interest. Because of their less favourable tolerability profiles, it is recommended that progestins and high-dose estrogens should generally be reserved for use later in the treatment sequence once the better-tolerated treatments have been exhausted.

Treatment options for premenopausal ABC

Although oophorectomy and ovarian irradiation remain as options for inducing permanent ovarian ablation, LHRHas are the preferred method of inducing a potentially reversible medical ovarian ablation in premenopausal patients with hormone receptor-positive disease. Goserelin is the most extensively studied LHRHa in advanced disease [42,43]. Tamoxifen is also

extensively used in the treatment of premenopausal women.

Goserelin

Pooled data from 228 pre- and perimenopausal patients with ABC included in various phase II open-label trials of goserelin first showed that it was effective in this setting [42,43]. Eighty-three of 228 patients (36%) experienced an objective response and a further 50% had no change in their disease with goserelin 3.6 mg (monthly depot) treatment. Median duration of response was 10.1 months (range: 0.9–36.8 months) and responses to goserelin were observed in all age groups and tumour types studied. Response rates were higher in patients with ER-positive and/or well differentiated tumours. Median overall survival was 26.5 months (range: 0.8–69.0 months) – a value that compares favourably with survival times reported for oophorectomy [44] or tamoxifen [45] in this patient group. These studies also showed that goserelin treatment was generally well tolerated with side effects mostly related to the pharmacological effects of estrogen suppression. Hot flushes and decreased libido were the most common adverse events, whereas other effects such as vaginal dryness or headache occurred much less frequently. The goserelin depot injection was also well tolerated locally.

Goserelin plus tamoxifen

Goserelin 3.6 mg alone has also been compared with a combination of goserelin 3.6 mg/month plus tamoxifen 40 mg/day as a first-line treatment in 318 pre- and perimenopausal patients with ABC [46]. In the overall population, there were no significant differences between groups with respect to objective response rates (31% versus 38%, respectively) or median overall survival (29.3 months versus 32.3 months, respectively), however, there was a benefit in favour of the combination in median TTP (5.3 months versus 6.5 months, respectively). Interestingly, in the subgroup of patients who had only skeletal metastases at entry ($n = 115$), significant differences in objective response, TTP and overall survival were seen in favour of the combination group. However, in a meta-analysis of four studies of an LHRHa versus an LHRHa plus tamoxifen, the combination showed significant benefits in objective response (39% versus 30%; $p = 0.03$), median progression-free survival (8.7 months versus 5.4 months; $p < 0.001$) and median overall survival (34.8 versus 30.0 months; $p = 0.02$) [47]. These data led to the recommendation that an LHRHa plus tamoxifen should be the standard regimen for premenopausal women with hormone-sensitive ABC [48]. The tolerability profile of the combination appears similar to that of goserelin alone [46].

Chemotherapy

In the past, chemotherapy was the preferred first-line treatment for all patients with ABC and was associated with objective response rates of 40–60% [49], which is higher than the response rate observed with endocrine therapy. However, the median duration of response usually ranged from 6 months to a maximum of 10 or 12 months [49,50], which is generally less than that observed with endocrine regimens [42,43]. For example, the median duration of response in 159 patients receiving goserelin plus tamoxifen was 13.6 months with a range of 2.8–49.7 months [46]. This indirect comparison may suggest that although initial responses may be higher in patients receiving chemotherapy for ABC, they are more durable in patients receiving endocrine treatment. Furthermore, for patients receiving goserelin there is a possibility that fertility can be regained after treatment cessation, wheras premenopausal women receiving chemotherapy often become permanently amenorrheic.

Treatment sequencing for premenopausal patients with ABC depends on any prior treatments received (and responses to such treatments) and also on whether or not the patient becomes postmenopausal (naturally or as a result of treatment) during initial treatment, which may open up further options.

Current treatment guidelines for ABC

The National Cancer Institute (NCI), European Society for Mastology (EUSOMA) and the National Comprehensive Cancer Network (NCCN) all support the use of AIs as initial therapy in postmenopausal patients with ABC [48,51,52]. However, beyond the first-line setting, there appears to be little consensus as to the recommended sequencing of endocrine therapies for ABC, particularly in postmenopausal women. Ovarian ablation is the therapy of choice for premenopausal patients with hormone receptor-positive disease.

NCI

Guidelines from the NCI support the use of third-generation AIs over tamoxifen as first-line ABC treatments for postmenopausal women [51]. Second-line hormonal treatment with AIs or fulvestrant is

recommended for women with ER-positive or ER-unknown tumours, soft tissue metastases only, or those who have received antiestrogen therapy within the last year. Other options include megestrol acetate, estrogens and androgens – NCI state that the optimum sequence of these treatments is unknown. For premenopausal women with ABC, initial treatment should include ovarian ablation (with surgery, radiotherapy or using an LHRHa). They also suggest that an LHRHa plus tamoxifen may be an option although, they believe that data for such combinations versus an LHRHa alone have been inconsistent.

NCCN

NCCN guidelines suggest that if a postmenopausal woman with ABC has not received antiestrogen treatment within the last year, they should be given a third-generation AI or antiestrogen as first-line treatment [52]. Premenopausal women should receive ovarian ablation or suppression plus endocrine therapy as for postmenopausal women. Another option for premenopausal women is to use an antiestrogen alone as tamoxifen has been shown to have similar efficacy to oophorectomy in some studies [53,54]. If a patient has received antiestrogen treatment within the last year, or following first-line ABC treatment, suggested second-line treatments (depending on initial treatment) include AIs, fulvestrant or tamoxifen/toremifene. The use of megesterol acetate, fluoxymesterone or ethinyl oestradiol is also supported.

EUSOMA

As with the above guidelines, EUSOMA support the use of third-generation AIs as first-line treatment in postmenopausal patients although antiestrogens should also be considered as an option [48]. However, AIs should be considered mandatory in patients who have a past history of thrombotic events and are also strongly recommended as initial therapy in those who have received tamoxifen adjuvant therapy (and vice versa). Crossover second-line treatment is recommended for patients receiving an AI or tamoxifen as initial therapy with subsequent suggested treatments including fulvestrant, megestrol acetate, or medroxyprogesterone acetate. Other options include fluoxymesterone or diethylstilboestrol. Third-line endocrine therapy should be offered in preference to chemotherapy in patients experiencing clinical benefit with second-line treatment. For premenopausal patients, combination treatment with an LHRHa plus tamoxifen is recommended as first-line therapy for hormone-sensitive ABC. The second-line treatment of choice for such patients is continued ovarian suppression with an LHRHa but replacing tamoxifen with a third-generation AI. Updates to these guidelines are currently awaited.

Future possibilities

There is a suggestion from preclinical studies that the efficacy of antiestrogens may be increased in a low estrogen environment such as that produced with AIs [55,56]. The combination of anastrozole and tamoxifen was evaluated as part of the ' Arimidex' , Tamoxifen, Alone or in Combination (ATAC) trial but was found to have similar efficacy to tamoxifen alone and to be less effective than anastrozole alone [24]. This may be due to the fact that anastrozole levels were found to be lower in patients receiving combination treatment indicating the presence of a drug-drug interaction between these agents. Another potential explanation may be that in the low-estrogen environment, the estrogen agonist activity of tamoxifen may become more dominant. It will be interesting to see whether substituting tamoxifen with a ' pure' antiestrogen such as fulvestrant in this combination will fulfil the promise such combinations have shown in preclinical studies. Two phase III trials (SOFEA and South-West Oncology Group [SWOG] study S0226) are currently investigating the potential of this combination in patients progressing on prior non-steroidal AIs.

Depending on tumour profile e.g., expression of HER2, epidermal growth factor receptor (EGFR), or vascular endothelial growth factor (VEGF) receptor, combination treatment with hormonal agents plus novel biological therapies may also be a possibility. Potential candidates for inclusion in such combination treatment strategies include the HER2-targeting agent trastuzumab (' Herceptin') and the EGFR inhibitor gefitinib (' Iressa'). It is hypothesised that combination of these agents with an antiestrogen may delay the onset of resistance by interfering with ER-growth factor receptor cross-talk. Several trials in postmenopausal patients with ABC are underway assessing the combination of fulvestrant or anastrozole with trastuzumab or gefitinib.

Although AIs are very effective treatments for postmenopausal women, they do not reduce estrogen levels sufficiently to be effective as monotherapy in premenopausal women with breast cancer because of the high level of ovarian estrogen production. However, it is possible that premenopausal women could also benefit from these agents if they were given in combination with ovarian ablation in a

similar way to tamoxifen is used in combination with goserelin in many patients. Phase II data for goserelin in combination with an AI (mainly anastrozole) in premenopausal patients with ABC has so far been encouraging [57–59] and several adjuvant trials in early breast cancer are now underway. This combination is also supported in some of the current treatment guidelines for premenopausal patients with breast cancer [48].

Summary

New standards in first-line ABC and adjuvant treatments are necessitating changes in subsequent endocrine treatment sequencing, particularly in postmenopausal patients. Several large trials are now underway to answer the important question as to what are the most appropriate agents for use following AI failure. Further developments in tumour profiling may also aid treatment decision-making and allow for more targeted, individualised management approaches. However, for the foreseeable future, treatment of ABC will remain palliative rather than curative and so the tolerability profiles of potential treatments as well their impact on quality of life should be reviewed in addition to comparative efficacy data.

Acknowledgements

We would like to thank Dawn Batty, PhD from CMC Ltd, who provided medical writing support.

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