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REVIEW

Postmenopausal advanced breast cancer: Options for therapy after tamoxifen and aromatase inhibitors

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Summary All patients receiving endocrine treatment for advanced breast cancer (ABC) eventually progress, resulting in a need for new therapies that lack cross-resistance with existing agents. Oestrogen receptor (ER) modulators such as toremifene and raloxifene have poor efficacy following tamoxifen failure, whereas the non-steroidal aromatase inhibitors (AIs), anastrozole and letrozole and the steroidal AI exemestane are effective. Fulvestrant is a new ER antagonist with no agonist effects that is as effective as anastrozole in treating patients who have progressed on tamoxifen. AIs are replacing tamoxifen as first-line treatments for ABC and in the adjuvant setting, necessitating a re-evaluation of optimal sequencing. Preliminary data suggest that tamoxifen, exemestane and fulvestrant have activity in patients who have progressed on non-steroidal AIs and hence could be considered for use in this setting. Due to the apparent lack of cross-resistance between non-steroidal and steroidal AIs, non-steroidal AIs could also be effective following steroidal AI failure. Clinical trials are underway to assess the most appropriate treatment sequence following non-steroidal AI failure, with comparisons of fulvestrant and exemestane of major interest.

Introduction

Treatments for advanced breast cancer (ABC) are essentially palliative, therefore as well as proven efficacy the desired goal of treatment is a long duration of response and maintenance of quality of life. Endocrine therapies are generally the treatment of choice in patients with hormone receptor (HR)-positive ABC, as they are as effective as cytotoxic chemotherapy, but are better tolerated. Tamoxifen is a selective oestrogen receptor modulator (SERM) that has been the mainstay of

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endocrine treatment for more than 30 years. Although tamoxifen is an oestrogen receptor (ER) antagonist in breast tissue, it acts as an ER agonist in bone, endometrium and other tissues, thus offering a bone-protective effect,[1] but increasing the risk of endometrial cancer and thromboembolic events.[2,3] Other SERMs, such as droloxifene, idoxifene, toremifene and raloxifene, can also act as ER agonists, and clinical trials have shown they are not superior to tamoxifen in the first-line setting[4,5] and have poor efficacy following tamoxifen failure.[3]

Aromatase inhibitors (AIs) reduce systemic and tumour oestrogen concentrations in postmenopausal women by blocking the conversion of androgens to oestrogens. AIs can be divided into two main classes, non-steroidal AIs (anastrozole, letrozole and aminoglutethimide) and steroidal AIs (exemestane and formestane). The non-steroidal AIs can be further subdivided into the triazole derivatives (anastrozole and letrozole) and the aminoglutethimide-like compounds. All steroidal compounds are derivatives of androstenedione, the main substrate of aromatase.[6]

Third-generation AIs (anastrozole, letrozole and exemestane), are now replacing tamoxifen in the first-line advanced and adjuvant settings as they have superior efficacy and in some cases, tolerability advantages.[7–13]

All tumours eventually develop acquired resistance to endocrine agents and disease progression then occurs. High-dose oestrogens, such as diethylstilboestrol or ethinyl oestradiol, or progestins (such as megestrol acetate), may be effective following failure on tamoxifen and/or AIs, but their use is limited by their toxicity profiles. Although these agents may be a more convenient option than chemotherapy for patients who have progressed on conventional treatments, yet remain potentially responsive to hormonal manipulation. With the increasing use of AIs early in the treatment sequence, there is a need for new non-cross-resistant agents that are effective and well tolerated following tamoxifen and/or AI failure. Once integrated, these agents offer the potential to extend the endocrine treatment sequence, which may delay the use of cytotoxic chemotherapy and maintain good quality of life for the patient.

Fulvestrant

Fulvestrant is a new type of ER antagonist that, in contrast to tamoxifen and other SERMs, has no agonist effects (Fig. 1).[14,15] Fulvestrant has a novel mode of action; it binds, blocks and degrades the ER and consequently lacks cross-resistance with other endocrine agents.[14,16–20]

Fulvestrant competes with oestradiol for binding to the ER and has a binding affinity >35 times stronger than that of tamoxifen and 89% that of oestradiol.[14] Its steroidal structure prevents ER dimerisation and blocks nuclear localisation of the receptor.[16] Any fulvestrant-ER complexes that do enter the nucleus are transcriptionally inactive, because both activating functions of the ER (AF1 and AF2) are disabled, which is in contrast to tamoxifen and other SERMS that only inactivate AF2 and therefore possess partial agonist activity (Fig. 1).

The fulvestrant–ER complex is unstable, resulting in accelerated degradation of the ER protein compared with oestradiol- or tamoxifen-bound receptors.[18,19] This results in a downregulation of the ER and a subsequent inhibition of oestrogen signalling, resulting in reduced levels of progesterone receptor[21] and inhibition of the expression of genes associated with tumour progression, invasion, metastasis and angiogenesis.[22]

Tamoxifen-resistant disease

Efficacy of SERMs

The objective response rates in a Phase II crossover study involving 66 postmenopausal women with advanced HR-positive breast cancer who received toremifene 240 mg/day or tamoxifen 40 mg/day as first-line treatment were 29% and 42%, respectively.[23] Following disease progression on first-line toremifene or tamoxifen, 44 patients were switched to the comparator agent, but no responses were observed, indicating that toremifene and tamoxifen are cross-resistant in patients with ABC.[23] Clinical studies evaluating the efficacy of other SERMs, such as droloxifene, idoxifene and raloxifene, have shown that these agents also have minimal activity in tamoxifen-resistant disease.[3]

Efficacy of AIs

Third-generation AIs, such as anastrozole, letrozole and exemestane, are effective following tamoxifen failure.[11,24–26] In randomised, double-blind trials, the clinical benefit rates (complete response, partial response or stable disease for $\geqslant 24$ weeks) range from 27% to 37% with these AIs.[11,24,25]