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Editorial Comment

Fulvestrant – ready to start its journey in the breast cancer adjuvant endocrine world?

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For hormone-responsive metastatic breast cancer patients with non-life-threatening disease, endocrine therapy has long been preferred to cytotoxic chemotherapy because of its excellent efficacy and side-effect profile. For the last 20 years, tamoxifen has been the mainstay of endocrine treatment. However, at the same time, one has witnessed the development of a growing number of new endocrine agents and their integration into clinical practice. The sequential use of these new agents, with their different mechanisms of action and partial lack of cross-resistance to tamoxifen, has proved invaluable in the palliative setting, allowing for the extension of hormonal therapy after patients have progressed on tamoxifen.

The latest addition to the armamentarium for treating advanced endocrine-responsive breast cancer is the pure anti-oestrogen, fulvestrant (Faslodex®; AstraZeneca). Fulvestrant downregulates and degrades the oestrogen receptor (ER), resulting in decreased activity in the ER pathway and reduced expression of the progesterone receptor (PR) [1]. Unlike tamoxifen, it has no agonist effects. Preclinical and clinical observations confirm a lack of cross-resistance with tamoxifen, with fulvestrant exhibiting anti-tumour activity in tamoxifen-resistant MCF-7 cell lines and in women with disease progression on tamoxifen [2,3]. Subsequently, the results of two large phase III trials (Trial 0020, 0021) comparing fulvestrant with anastrozole in tamoxifen-resistant advanced breast cancer demonstrated that fulvestrant was as effective as anastrozole in this setting, with similar tolerability and quality of life effects [4,5].

Fulvestrant's current clinical efficacy and tolerability are comprehensively discussed in this issue by Robertson and colleagues [6]. The authors also speculate on its potential future position in the endocrine sequence cascade given the somewhat disappointing results of the fulvestrant's most recent trial [7]. Contrary to all expectations, a double-blind, randomised, double-dummy trial found that fulvestrant was possibly less effective than tamoxifen. This was despite extensive preclinical data that reported fulvestrant to be a more effective growth inhibitor of ER-positive MCF-7 human breast cancer cells, and a more potent suppressor of growth in established tumour xenografts in mice models [8,9]. In a recent study of gene expression profiles of ER-responsive genes derived from MCF-7 cells, most of these genes were completely downregulated by fulvestrant, in contrast to tamoxifen where some genes remained active [10]. Additionally, these clinical results were difficult to explain given the evidence accumulated thus far: that aromatase inhibitors (AIs) are superior to tamoxifen in the first-line setting in metastatic disease leading to AIs becoming widely used for this purpose [11,12] and that fulvestrant is as effective as an AI as second-line therapy. There were few plausible explanations for the unanticipated result of this study. The trial was adequately powered, and well conducted. There was a small imbalance in the number of patients assigned to treatment, but the groups were well matched for baseline patient characteristics. The pharmacokinetics of fulvestrant has been proposed as one potential explanation, because steady-state concentrations of the currently used dose and schedule take a long time to be reached; however, the dose and schedule used were the same as in Trial 0020. Further studies are planned using a

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loading dose, but for the moment, fulvestrant's merit in the first-line setting is unclear.

Perhaps the heterogeneity of breast cancer has contributed to these results. Unrecognised molecular heterogeneity can indeed significantly underpower clinical trials aimed at determining the effectiveness of a new therapy, particularly if the benefit in responding patients is weakened by a non-existent or negative effect in non-responding ones [13]. High throughput transcriptional profiling is improving our understanding of the molecular biology of breast cancer and has already demonstrated that distinct phenotypes exist within ER-positive breast cancers [14,15]. These subgroups may exhibit varying sensitivity to endocrine manipulation [16–18]. As outlined by Robertson and colleagues an exploratory analysis has suggested greater activity of fulvestrant compared with tamoxifen in tumours expressing both ER and PR; however, such unplanned retrospective subset analysis can only be hypothesis-generating. In any event, the complexity of the ER pathway, with over 100 individual genes can no longer be ignored [19].

In parallel, increased understanding of the interplay between ER and growth factor networks is offering explanations for the development of endocrine resistance and new ideas for delaying or circumventing it. This cross-talk can occur in both directions and, importantly, appears to involve a retained and functional ER. On the one hand, tamoxifen and oestrogen deprivation may upregulate the expression of epidermal growth factor (EGF) and c-erbB2 receptors. One the other, ER may undergo ligand-independent phosphorylation and activation via a number of intracellular mitogen-activated protein kinases [20,21]. Lastly, ER may play a role in the non-nuclear oestrogen-dependent signalling via interaction with the Akt survival pathway or the stress activated protein kinase/c-Jun-NH(2)-terminal kinase pathway [20] . In all three circumstances, hormone-independent growth can take place and it is obvious then, that a drug able to downregulate ER, such as fulvestrant has tremendous potential if introduced in the endocrine sequence at the right time. As discussed by Robertson and colleagues the optimal timing for this introduction remains to be found, but is likely to vary according to individual tumour characteristics. This underscores the importance of translational research in the ongoing clinical trials that examine the most advantageous positioning of fulvestrant in the endocrine treatment sequence for advanced breast cancer. A subgroup for which earlier positioning of fulvestrant might be appropriate are the HER2-overexpressing ER-positive tumours, given the likelihood of early onset of ligand-independent ER activation [20].

The growing understanding of endocrine resistance mechanisms has also led to the concept that combining signal transduction inhibitors and endocrine agents might further enhance the therapeutic response to endocrine therapy: numerous clinical trials testing this concept are in progress. In particular, the combination of fulvestrant and gefitinib, which may inhibit receptor cross-talk, has been found to be effective in delaying endocrine resistance in cell lines [22,23]. Similarly, the combination of fulvestrant and the novel c-erbB2 targeting antibody, trastuzumab, may be more effective in HER-2 overexpressing ER-positive breast cancers than either therapy alone.

While the optimal sequence of endocrine agents in women with advanced breast cancer is still under investigation, it is fascinating to see early data supporting a move towards the use of sequential endocrine therapies in the adjuvant setting: indeed, two large randomised trials have shown that a sequence of tamoxifen followed by an AI is superior in terms of disease-free survival to five years of adjuvant tamoxifen [24,25]. The National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) MA.17 (BIG 1-97) trial was the first to demonstrate a benefit for sequential letrozole after five years of adjuvant tamoxifen [24]. In this study, 5187 postmenopausal women were randomly assigned to letrozole or placebo after 5 years of tamoxifen. With a median follow-up of 2.4-years, a pre-planned interim analysis reported a significant difference in the four-year disease-free survival (93% vs 87%, $P < 0.001$). Subsequently, the multicentre, double-blind, randomised Intergroup Exemestane Study (BIG 2-97) reported a benefit for exemestane after three years of adjuvant tamoxifen [25]. After a median follow-up of 30.6 months, at the planned second interim analysis, the group of patients receiving sequential exemestane was associated with a 4.6% significant absolute benefit in three-year disease-free survival (91.5% vs 86.8%, $P < 0.001$).

The pure anti-oestrogen fulvestrant offers further promising opportunities to these sequential endocrine therapeutic approaches in the adjuvant setting. With the above-mentioned encouraging data emerging from large randomised trials exploring sequencing and extended duration of endocrine agents in the adjuvant setting, it is tempting to speculate that fulvestrant may also have an important future role to play – perhaps as "extended adjuvant therapy" following a few years of an AI. These strategies have to be explored in the context of well-designed, clinical adjuvant trials that are also adequately powered to answer biological hypotheses. These trials will ultimately lead to further improvements in endocrine therapy tailoring and in the survival of women with endocrine-responsive breast cancer.

Conflict of interest statement

None declared.

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