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E22. Fulvestrant in 2004: current and future indications for breast cancer

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Fulvestrant is an oestrogen analogue. A bulky side-chain in the 7 α position of the parent oestrogen molecule inhibits activation of the oestrogen receptor (ER) and increases receptor turnover, thus markedly reducing the number of ERs per cancer cell. This mechanism of action differs from the selective oestrogen receptor modulators (SERMs) such that tamoxifen-bound ERs are not downregulated and are available to bind to endocrine response elements of target genes. This difference in mechanism of action between fulvestrant and SERMs is presumably why fulvestrant is highly active after tamoxifen failure. In the original phase II trial of 19 patients, approximately two thirds of patients had clinical benefit (CB) [1]. Subsequent trials where fulvestrant was compared with anastrozole after tamoxifen failure, indicated CB rates for fulvestrant of 44.6% [2] and 42.2% [3], respectively. In these trials, there were no significant differences between the activity of fulvestrant and anastrozole in tamoxifen failures. However, the proportion of patients who had CB for one year was 19.2% for fulvestrant and 13.9% for anastrozole ($P = 0.07$). A further randomised trial indicated that fulvestrant was equivalent to tamoxifen as first-line therapy for advanced disease in patients with hormone receptor +ve tumours [4]. Fulvestrant is therefore active after failure of tamoxifen or when used as first-line endocrine therapy for advanced breast cancer. Several groups have produced non-randomised data. In a study where fulvestrant was given after first-, second- or third-line endocrine therapy with a variety of agents ($n = 67$), the CB rate was 59.7%, with a median duration of response of six months. Responses were seen in patients with HER2+/ER+ tumours [5]. In another study of 44 previously endocrine-treated patients with advanced disease, the CB rate was 52% (L Petruzelka, Prague, University Karlovy). Endocrine therapy is effective when given after fulvestrant. In 35 patients who had CB on fulvestrant, the CB rate to subsequent endocrine therapy was 57%. In the same study, the CB rate was 43% ($n = 35$) in patients who had not responded to fulvestrant [6]. Another study showed that treatment with predominantly aromatase inhibitors (AI) after second-line fulvestrant produced CB in 25 out of 54 (46%) patients [7].

The studies outlined above indicate that fulvestrant is effective in some patients after one, two or three endocrine therapies. In addition, other endocrine therapies are effective after fulvestrant failure. Additional studies are required to evaluate precisely the position of fulvestrant in the sequence we use to treat advanced breast cancer. New phase II and III trials ($n \geqslant 8$) in over 3000 patients are either planned or are currently in progress (summarised in [8]). These are mainly evaluating fulvestrant versus a steroidal AI after failure on non-steroidal AIs or further phase II studies in advanced disease or as neoadjuvant therapy. At present, the available data indicate that, because there is a relative lack of cross-resistance between tamoxifen/aromatase inhibitors and fulvestrant, this agent should be regarded as an additional endocrine therapy to add to our sequence of treatments for advanced breast cancer.

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