survival benefit with exemestane was noted early in the course of treatment and survival curves continued to diverge over time. Exemestane was associated with similar or greater improvement in pain, tumour-related signs and symptoms, and quality-of-life endpoints compared with megoestrol acetate. Both treatments were well tolerated. The most common ($\geqslant 5\%$) drug-related adverse events (usually grade 1–2) were: for exemestane — hot flushes (12.6%), nausea (9.2%) and fatigue (7.5%); for megoestrol acetate — fatigue (10.3%), increased sweating (7.5%), increased appetite (5.8%), nausea (5.0%) and hot flushes (5.0%). Drug-related withdrawals (1.7 versus 5.0%; $P=0.011$), drug-related deaths (0 versus 0.7%), and weight gain $\geqslant 10\%$ (7.6% versus 17.1%: $P=0.001$) were more common with megoestrol acetate.

Exemestane significantly prolongs time to progression, time to treatment failure, and survival when compared with megoestrol acetate and should be considered as the standard treatment in postmenopausal women with ABC who fail on tamoxifen.

Acknowledgements

Supported in part by a grant-in-aid from Pharmacia & Upjohn.

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Faslodex (ICI 182780): an oestrogen receptor downregulator

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Abstract

Anti-oestrogen therapy, tamoxifen in particular, has revolutionised the treatment of breast cancer. However, the partial agonist activity of tamoxifen is associated with an increased risk of endometrial cancer and the acquisition by patients of tamoxifen-resistance. In an attempt overcome these negative aspects of tamoxifen therapy, 'pure' anti-oestrogens have been developed and are currently being investigated for the treatment of breast cancer.

Keywords: Tamoxifen; ICI 182780; RU 58668; EM-800; 'Pure' anti-oestrogen; Steroidal; Non-steroidal; SERM

The non-agonist 'pure' anti-oestrogens, have been developed to overcome the negative effects of the partial agonist activity of tamoxifen and related selective oestrogen receptor modulators (SERMs), on the endometrium and to avoid or, at least, postpone the development of resistance in breast cancer.

The most advanced of these agents, in terms of both pre-clinical and clinical evaluation, is the steroidal compound ICI 182780 [1,2]. ICI 182780 has a mode of action that is distinct from that of tamoxifen and the other related non-steroidal anti-oestrogens. Tamoxifen binds to and modulates the activity of the oestrogen receptor (ER) and this has led to the term selective oestrogen receptor modulator (SERM), while exposure to ICI 182780 leads to downregulation and loss of the ER [2]. This results in the complete abrogation of ER function. The inhibitory actions of pure anti-oestrogens on oestrogen-induced transcriptional events and subsequently on cell proliferation and survival exceed those achieved by anti-oestrogens with partial agonist activity [1]. ICI 182780 inhibits the growth of tamoxifen resistant cell lines [1], inhibits the uterotrophic effects of tamoxifen and doubles the duration of response seen in the MCF-7 human breast tumour model [3]. ER downregulation following treatment with ICI 182780, has been demonstrated in the clinic in postmenopausal

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0959-8049/00/$ - see front matter
PII: S0959-8049(00)00241-0

women with primary breast cancer [4,5]. In a small phase II study of 19 postmenopausal patients with advanced breast cancer (ABC) failing on tamoxifen therapy, 37% of patients achieved a partial response and a further 32% achieved disease stabilisation. The median duration of response was 26 months [6]. No negative effects were observed on the liver, brain or genital tract. These clinical data confirmed the lack of cross-resistance between ICI 182780 and tamoxifen and suggested a prolonged duration of tumour control. To date, there are no clinical data available for the effects of ICI 182780 on bone and only a small amount of data (from non-comparative studies) for effects upon lipid profiles and the endometrium.

However, ICI 182780 is being studied versus the non-steroidal aromatase inhibitor anastrozole and tamoxifen in two separate phase III studies as part of a large clinical programme involving postmenopausal women with ABC who have either failed on tamoxifen therapy or not received prior tamoxifen therapy.

Another steroidal anti-oestrogen believed to be devoid of any oestrogen-agonist activity is the Roussel compound RU 58668. It is structurally similar to ICI 182780 and possesses all the properties of a pure anti-oestrogen in pre-clinical studies [7]. At present there are no clinical data available for this anti-oestrogen, but the pre-clinical data for RU 58668 suggest that it could be used for the treatment of ER-positive patients who have failed prior tamoxifen therapy and in breast cancer prevention [7]. The non-steroidal anti-oestrogen EM-800, which was developed as an oral 'pure' anti-oestrogen and behaves as a 'pure' anti-oestrogen in relation to the breast, uterus, vagina and hypothalamo-pituitary-gonodal axis [8], has recently been shown to inhibit bone loss and to reduce serum cholesterol levels [8], and may in fact turn out to be SERM rather than a SERD. There are no published clinical data for this compound.

Thus, ICI 182780, clearly offers an effective alternative in the clinic for patients whose disease has become resistant to tamoxifen [6], and might be more effective than tamoxifen as a first-line endocrine therapy. The results of the phase III studies and the clinical effects of ICI 182780 on bone density and the serum lipid profile are awaited.

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Determination of tamoxifen and its metabolites in the endometrial tissue of long-term treated women

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Abstract

Concentrations of tamoxifen and its metabolites were analysed in the endometrium of 23 post-menopausal asymptomatic breast cancer patients who were on chronic tamoxifen therapy. Small endometrial samples were collected during diagnostic hysteroscopy. Analysis of both serum and tissue for these compounds was performed by mass spectrometry. Tamoxifen and its metabolites were

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PII: S0959-8049(00)00242-2