Exemestane improves survival compared with megoestrol acetate in postmenopausal patients with advanced breast cancer who have failed on tamoxifen: results of a double-blind randomised phase III trial

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Abstract

Exemestane is an aromatase inactivator. 769 Postmenopausal women with advanced breast cancer who had failed on tamoxifen were randomised to exemestane or megoestrol acetate in this double-blind trial. Objective response rate was similar between treatments. Median time to progression, time to treatment failure and overall survival was significantly longer with exemestane. Drug-related withdrawals and drug-related deaths were more common with megoestrol acetate. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Breast neoplasms; Aromatase; Enzyme inhibitor; Megoestrol acetate; Antineoplastic agents; Hormonal

The standard of care for hormonal therapy in postmenopausal women with advanced breast cancer (ABC) who experience failure of tamoxifen has shifted from megoestrol acetate to third generation aromatase inhibitors due to similar efficacy and improved tolerability of the latter [1,2]. Exemestane is a novel oral steroidal aromatase inactivator that acts by binding irreversibly to the aromatase enzyme. Subtle differences in the pharmacology of aromatase inactivators versus inhibitors suggest that inactivators may offer advantages [3].

The double-blind, randomised, multicentre trial recruited 769 postmenopausal women with ABC who experienced failure on tamoxifen. Patients with measurable or evaluable disease were randomised to exemestane 25 mg orally once daily or megoestrol acetate 40 mg orally 4 times daily. Efficacy and safety were evaluated. Baseline characteristics and prognostic factors were well balanced, including performance status, hormone receptor status, predominant disease site (visceral; exemestane, 57% megoestrol acetate, 59%) and measurable disease (78% for both groups). The medial overall duration of follow-up was 49 weeks. Intent-to-treat, peer reviewed efficacy results are shown in Table 1.

Exemestane produced a 23% relative reduction in the risk of death compared with megoestrol acetate. The

Table 1
Intent-to-treat, peer reviewed efficacy results

	Exemestane ($n=366$)	Megoestrol acetate ($n=403$)	*P* value
Response characteristic, %			
CR + PR	15.0	12.4	NS
Overall success[a]	37.4	34.6	NS
Time-dependent parameters (median) months			
Duration of CR + PR	17.7	16.5	NS
Duration of overall success	14.0	11.4	0.025
Time to progression	4.7	3.9	0.037
Time to treatment failure	3.8	3.7	0.042
Survival	Not reached	28.7	0.039

CR, complete remission; NS, not statistically significant; PR, partial response.

[a] Overall success is defined as CR + PR + SD $\geqslant$ 24 weeks.

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0959-8049/00/$ - see front matter
PII: S0959-8049(00)00240-9

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