

Recent advances in endocrine therapy of breast cancer

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Regression of advanced breast cancer as a result of endocrine therapy was first described over 100 years ago.¹ Interest in this form of treatment increased when treatment with the antioestrogen tamoxifen after surgery for breast cancer was shown to improve patients' survival.^{2,3} Treatment also reduced the incidence of new cancers in the contralateral breast, which has led to a number of trials of tamoxifen as a preventive measure in women at high risk.⁴ New, potentially more active endocrine agents are now being introduced into clinical practice. In this review we outline the mechanism of action of these treatments and summarise recent results of clinical trials assessing their efficacy in comparison with older drugs; we also speculate about future trends in endocrine therapy and summarise clinical trials in progress.

Methods

This article is based, in part, on our own collaborative experimental work and close association with pharmaceutical companies developing new endocrine agents. Additional reviews and original articles were obtained from searches of oncological journals. Recent data were obtained from presentations at the May meeting of the American Society for Clinical Oncology.

Mechanism of action of newer endocrine therapies

Breast cancer cells that are endocrine dependent need oestrogen to proliferate.⁵ Most endocrine therapies either block the binding of oestrogen to its receptor in the nucleus of responsive cells or reduce serum and tumour concentrations of oestradiol. In postmenopausal women androgens (mainly from the adrenal glands) are converted into oestrogens by the enzyme aromatase, which is present in a range of tissues and is found in 60-70% of breast carcinomas.⁶

The trend for endocrine therapies over the past 100 years has been towards simpler and more widely applicable treatments. Originally pharmacological doses of oestrogens were used to block the proliferative effect of oestrogen, but now this is achieved with tamoxifen.² Oestrogen concentrations were reduced by surgery (oophorectomy, adrenalectomy, and hypophysectomy), but now analogues of luteinising hormone releasing hormone, which effectively ablate ovarian steroidogenesis, may be used in premenopausal women; aromatase inhibitors are used in postmenopausal women.

Summary points

Many new hormonal therapies that either antagonise oestrogen (antioestrogens) or inhibit its synthesis (aromatase inhibitors) are under intense clinical study

Phase III trials including nearly 3000 patients have shown that new aromatase inhibitors have better tolerability and improved efficacy, including survival gains, than the other second line endocrine agents, megestrol acetate and aminoglutethimide

New antioestrogens have less agonist activity than tamoxifen; it is not yet known if this will translate to important clinical gains

Trials involving many thousands of breast cancer patients are under way to compare these exciting new agents with tamoxifen as first line therapy, both as adjuvant treatment and for advanced disease

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Antioestrogens¹

Pharmacology

Tamoxifen is an antioestrogen but has a complex pharmacology, partly due to its metabolism to numerous biologically active compounds. It is an oestrogen agonist-antagonist that depends on its competitive binding to oestrogen receptors. Several other biochemical pathways are affected by tamoxifen, but their clinical importance is doubtful; the predominant importance of the oestrogen receptor dependent pathway is supported by clinical responses to tamoxifen being largely confined to tumours positive for oestrogen.

In an oestrogenic environment tamoxifen stops the proliferation of breast cancer cells that bind to oestrogen receptors. But if oestrogen concentrations are low, tamoxifen may act as an oestrogen agonist and lead to the proliferation of these cells, at least in model systems. Reducing this agonist activity has become the major target of new drugs and has led to the development of non-steroidal drugs that act like tamoxifen, as well as steroidal compounds that are derivatives of oestradiol.⁷ These two groups differ in their interaction with oestrogen receptors. The non-steroidal com-

pounds bind to oestrogen receptors, leading to their activation and dimerisation and their binding to specific oestrogen response elements on DNA which causes transcription of oestrogen responsive genes. A complex series of coactivators and corepressors can also substantially modify the agonist or antagonist response to the complex of drug and oestrogen receptor. Drugs of this type which are in or have recently completed phase III development include toremifene, droloxifene, TAT-59, and idoxifene. Other than toremifene, each of these has improved antagonist-agonist balance in standard model systems such as the immature rat uterine weight test.^{8,9}

In contrast, the steroidal antagonists (exemplified by ICI 182780, Faslodex) have been characterised as pure antagonists, as in their case the complex of drug and oestrogen receptor is effectively inactive. There is debate as to whether this is due to lack of dimerisation in the oestrogen receptor or a lack of binding to oestrogen response elements, but it seems clear that the activating functions are blocked and that the stability of the oestrogen receptor is reduced such that the oestrogen receptor content of the tumour is greatly reduced.

Both Faslodex and idoxifene are more effective antitumour agents than tamoxifen in animal model systems, and both show activity in cells and tumours that have become resistant to tamoxifen.⁷

Conventional clinical pharmacology of the new antioestrogens has not been instructive for their clinical development because there are no good surrogate markers of their activity against cancer. Their clinical development is being helped by a novel approach, in which pathological markers of proliferation and apoptosis are measured in primary breast carcinomas after short term, presurgical treatment with the drugs before surgery.^{10,11}

Tamoxifen's oestrogen agonist activity is advantageous on some tissues other than breast cancer, including bone and liver, but not endometrium. Experimental evidence indicates that chemical modifications can enhance the therapeutic efficacy and tolerability of non-steroidal compounds and lead to a group of compounds called SERMS (selective oestrogen receptor modifiers). An example is raloxifene, which is in its late stages of development as an antiosteoporotic agent; it lacks the breast and endometrial stimulation of oestrogen. New compounds of this type will soon enter clinical development for breast cancer treatment and are candidates for breast cancer prevention strategies.¹²

Table 1 Recently reported phase III and randomised phase II trials of new non-steroidal antioestrogens

Drug (ref)	Dose (mg/day)	No of patients	Response (%) [*]	Comment
Tamoxifen versus toremifene ¹⁴	20	215	19	Phase III trial as first line treatment in advanced disease
	60	221	21	
	200	212	22	
Droloxifene ¹⁵	20	84	30	Randomised phase II trial
	40	88	47	
	100	96	44	
TAT-59 ¹⁶	10	15	15	Randomised phase II trial
	20	11	55	
	40	13	31	

^{*}Complete response plus partial response.

Clinical results

Tamoxifen is the "gold standard," but its agonist effect may stimulate tumour growth and cause treatment to fail.¹³ The newer non-steroidal antioestrogens have been developed because (with the exception of toremifene) they have reduced agonist activity.

Table 1 shows some recent studies of new antioestrogens. A phase III trial found that toremifene was not superior to tamoxifen.¹⁴ The analogue droloxifene seemed active in phase II trials when used at doses of 20-100 mg/day, as did the Japanese drug TAT-59.^{15,16} We need more information from phase II trials about idoxifene and data from phase III trials comparing tamoxifen with droloxifene, TAT-59, and idoxifene.

The pure antioestrogen ICI 182780 (Faslodex) showed little agonist activity in preclinical tests and in the only clinical trial in advanced breast cancer performed to date.¹⁷ Notably, it is active when given after failure of tamoxifen and produces remissions of two years whereas standard second line endocrine therapy usually gives a one year median duration of response. Again, randomised data are required to confirm these promising preliminary data.

Aromatase inhibitors

Pharmacology

Using aromatase inhibition to suppress oestrogen synthesis was developed as a treatment for breast cancer over 20 years ago.¹⁸ During the intervening period many inhibitors have been developed. Plasma oestrogen concentrations have been widely used to assess pharmacological effectiveness, but such assays have not been sufficiently sensitive to provide reliable comparisons between inhibitors. Isotopic methods that directly measure the inhibition of enzyme activity throughout the body have provided more useful comparative data. There is no evidence that any of the inhibitors differentially inhibit aromatase in different tissues. The inhibitors may be considered as two families, steroidal and non-steroidal.

Non-steroidal

All of the non-steroidal agents are active orally. Until 1992 the only widely available inhibitor was aminoglutethimide. This drug inhibits several cytochrome P450 enzymes, including some involved in steroidogenesis, and has been widely used in breast cancer in combination with replacement doses of glucocorticoid as a "medical adrenalectomy." When aminoglutethimide's clinical effectiveness was shown to be due to its inhibition of aromatase, this enzyme became a therapeutic target. The side effects of aminoglutethimide (mainly skin rashes and neurological symptoms), its lack of specificity (requiring replacement glucocorticoid), and its relatively low potency have been targets for pharmaceutical improvement and have been well met by the most recent drugs.

A series of triazole derivatives, anastrozole (Arimidex),^{19,20} letrozole (Femara),^{21,22} and vorozole (Rivizor)^{23,24} have all been shown to have excellent selectivity for aromatase in preclinical models, and this has been confirmed in clinical studies. Their intrinsic potency is considerably greater than that of aminoglutethimide. In patients, aminoglutethimide inhibits total body aromatisation by about 91%, while anastro-

Table 2 Recently reported phase III trials which compare standard second line endocrine therapy with the new triazole inhibitors

Drug	Dose (mg/day)	No of patients	Proportion (%) of patients responding*	Median survival (months)	Comment
Anastrozole ^{19,20}	1	263	42.2 (+SD)	26.7	
Anastrozole	10	248	39.9	25.5	Significant survival advantage with anastrozole 1 mg
Megestrol acetate	160	253	40.3	22.5	
Letrozole ²¹	0.5	188	12.8 (-SD)	22.6	Trend for survival advantage with letrozole 2.5 mg
Letrozole	2.5	174	23.6	26.1	
Megestrol acetate	160	189	16.4	23.5	
Letrozole ²²	0.5	Total 555	16.7 (-SD)	No data	Trend for survival advantage for both doses of letrozole
Letrozole	2.5		17.8		
Aminoglutethimide plus hydrocortisone	500		11.2		
	30				
Vorozole ²³	2.5	277	47 (+SD)	25.7	Trend for survival advantage with vorozole
Aminoglutethimide plus hydrocortisone	500	279			
	30	279	37	21.7	
Vorozole ²⁴	2.5	190	10.5 (-SD)	28.0	
Megestrol acetate	160	185	7.6	28.7	

*Complete response plus partial response; SD=stable disease (≥ 6 months).

zole and letrozole, at their recommended doses of 1 mg/day and 2.5 mg/day, inhibit by about 97% and >99%, respectively.²⁵ In many patients this results in plasma oestrogen concentrations which even the most sensitive immunoassays cannot detect.²⁵

Steroidal

Two of the steroidal agents, formestane and exemestane, have undergone considerable clinical development. Formestane (4-hydroxyandrostenedione; Lentaron) was the first selective inhibitor to be licensed.²⁶ It is given by intramuscular injection because it is metabolised too quickly if taken orally. It is more specific than aminoglutethimide but does not have more pharmacological activity. Exemestane is orally active and seems to be selective at clinical doses.²⁷ No data have been published on its effects on whole body aromatisation. The only pharmacological data from a randomised comparison between any of the inhibitors showed the superiority of anastrozole over formestane in suppressing plasma oestradiol.²⁸

Clinical results

Table 2 shows the results of recent randomised clinical trials comparing aromatase inhibitors with standard second line endocrine therapy (after tamoxifen). The trials for letrozole and anastrozole had three arms: two doses of the new aromatase inhibitor compared with either the progestogen (megestrol acetate) or the old aromatase inhibitor (aminoglutethimide). Vorozole has been tested against these same comparators at a single dose in trials with two arms.^{25, 24}

All three of the new non-steroidal triazole derivatives (anastrozole, letrozole, and vorozole) and the steroidal derivative exemestane have shown minimal toxicity. In particular, they do not produce the troublesome weight gain of megestrol acetate nor the rash and neurological symptoms of aminoglutethimide. Since all four compounds are specific aromatase inhibitors, glucocorticoid replacement is not required.

In general, all the trial results point in the same direction. Overall response rates with the new and the old treatments are similar. Responses have been reported as either complete and partial remissions or as complete and partial remissions and stable disease for at least six months. The latter reports are more

logical since stable disease gives equivalent palliation and survival.²⁹ The durations of response of the new agents have tended to be longer than the old, but even more important are the survival advantages shown by new agents. The trial with the longest follow up shows that anastrozole 1 mg has significant survival advantage over megestrol acetate 160 mg,²⁵ and the other trials show trends towards survival advantages. The uniformity of this difference suggests that these trends are likely to become significant with further follow up.

Trials in progress

The introduction of new agents and the results of trials generate new questions and the need for new clinical trials. Table 3 outlines trials in progress or which are due to start shortly.

We need to know whether the new non-steroidal antioestrogens (idoxifene, droloxifene, TAT-59) that show better preclinical characteristics than tamoxifen are better clinically. Large trials comparing all three new agents with tamoxifen are ongoing. The pure antioestrogen Faslodex looks highly promising in vitro, in animal studies, and in early phase II tests. However, phase II studies are notoriously unreliable in

Table 3 Clinical trials using endocrine therapy projected or in progress in early (adjuvant) and advanced breast cancer (phase III)

Treatment	Adjuvant breast cancer	Advanced breast cancer
Receptor blockade:		
Idoxifene	—	20 mg v 40 mg v 20 mg tamoxifen
Droloxifene	—	20 mg v 20 mg tamoxifen
TAT-59	—	20 mg v 20 mg tamoxifen
Faslodex (ICI 182780)	—	125 mg v 250 mg v 20 mg tamoxifen
Oestrogen receptor:		
Anastrozole	Tamoxifen Anastrozole Both	Anastrozole Tamoxifen
	Tamoxifen 2 years	Tamoxifen 3 years Anastrozole 3 years
Letrozole	Tamoxifen Letrozole	Letrozole Tamoxifen
Vorozole	Tamoxifen 5 years	Placebo 5 years Vorozole 5 years
Exemestane	Tamoxifen 2-3 years	Tamoxifen 2-3 years Exemestane 2-3 years

Table 4 Past, present, and potential future treatment of advanced breast cancer by blocking oestrogen receptor or reducing concentrations of oestrogenic steroids in postmenopausal patients

	Oestrogen receptor blockade	Reduction of oestrogen concentrations	
Past	High dose oestrogens	Hypophysectomy	
		Adrenalectomy	
		Aminoglutethimide	
Present	Tamoxifen	Oophorectomy	
		4-OH androstenedione	
		Anastrozole	
		Letrozole	
Future	Non-steroidal:	Luteinising hormone releasing hormone agonists	
		Droloxifene	Vorozole
		Idoxifene	Exemestane
		TAT-59	Sulphatase inhibition
		Selective oestrogen receptor modulators (eg raloxifene)	Luteinising hormone releasing hormone antagonists
		Steroidal:	ICI182780 (Faslodex)

predicting superiority over old agents. Thus the recently started study comparing Faslodex with anastrozole as second line endocrine therapy for advanced disease and the comparison of Faslodex with tamoxifen as first line treatment that is to start late in 1997 are highly important.

The success of the new aromatase inhibitors as second line treatments for advanced disease has led to the initiation of trials using these drugs as first line agents for advanced disease and comparing them to tamoxifen as adjuvant therapies. The optimal duration for tamoxifen as an adjuvant seems to be five years. Studies are in progress or shortly to start in which a changeover to an aromatase inhibitor after two or three years of tamoxifen is compared with continuous tamoxifen (table 3). Change to an aromatase inhibitor after five years of tamoxifen in comparison with stopping all treatment is also being tested.

Conclusions

Although the principles of endocrine therapy have not changed over the past 100 years, new methods have resulted in less toxic and more widely applicable treatments (table 4). Also, for the first time, we have begun to see improvements in the effectiveness of treatment in terms of response duration and, most importantly, survival.

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- 1 Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma. Suggestions for a new method of treatment with illustrative cases. *Lancet* 1896;2:104-7.
- 2 Cole MP, Jones CTA, Todd IDH. A new anti-oestrogenic agent in late breast cancer: an early clinical appraisal of ICI 146474. *Br J Cancer* 1971;25:270-5.
- 3 Early Breast Cancer Trialists Co-operative Group (EBCTCG). Systemic treatment of early breast cancer by hormonal, cytotoxic, or immunotherapy. *Lancet* 1992;339:1-15,71-85.
- 4 Cuzick J, Baum M. Tamoxifen and contralateral breast cancer. *Lancet* 1985;ii:282.
- 5 Lippman M, Monaco ME, Bolan G. Effects of oestrone, estradiol and oestrin on hormone responsive human breast cancer in long term tissue culture. *Cancer Res* 1977;37:1901-7.
- 6 Miller WR. Endocrine treatment for breast cancers: biological rationale and current progress. *J Steroid Biochem Mol Biol* 1990;37:467-80.
- 7 Howell A, DeFriend D, Robertson J, Blamey R, Walton P. Response to a specific anti-oestrogen (ICI 182780) in tamoxifen-resistant breast cancer. *Lancet* 1995;345:29-30.

- 8 Chander SK, Newton C, McCague R, Dowsett M, Luqmano Y, Coombes RC. Pyrrolidine-4-iodotamoxifen and 4-iodotamoxifen, new analogues of the anti-oestrogen tamoxifen for the treatment of breast cancer. *Cancer Res* 1991;51:5851-8.
- 9 Wakeling AE, Dukes M, Bowler J. A potent specific pure antiestrogen with clinical potential. *Cancer Res* 1991;51:3867-73.
- 10 De Friend DJ, Howell A, Nicholson RI, Anderson E, Dowsett M, Mansel RE, et al. Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer. *Cancer Res* 1994;54:408-14.
- 11 Ellis PA, Saccani Jotti G, Johnston SRD, E Anderson, A Howell, R A'Herne, et al. Induction of apoptosis by tamoxifen and ICI 182780 in primary breast cancer. *Int J Cancer* 1997;72:608-11.
- 12 Sato M, Glasebrook AL, Bryant HU. Raloxifene: a selective estrogen receptor modulator. *J Bone Miner Met* 1994;12(suppl 2):S9-20.
- 13 DeFriend DJ, Anderson E, Bell J, Wilks DP, West CML, Mansel RE, et al. Effects of 4-hydroxytamoxifen and a pure antiestrogen (ICI 182780) on the clonogenic growth of human breast cancer cells in vitro. *Br J Cancer* 1994;70:204-11.
- 14 Hayes DF, Van Zyl JA, Hacking A, Goedhals L, Bezwoda WR, Mailliard JA, et al. Randomised comparison of tamoxifen and two separate doses of toremifene in postmenopausal patients with metastatic breast cancer. *J Clin Oncol* 1995;13:2556-66.
- 15 Rauschning W, Pritchard KI. Droloxifene, a new antiestrogen: its role in metastatic breast cancer. *Breast Cancer Res Treat* 1994;31:83-94.
- 16 Tominaga T. Early phase II clinical study of TAT-59 (new antiestrogen) in patients with advanced breast cancer. 19th International Congress of Chemotherapy, Montreal, Canada, 1995.
- 17 Howell A, DeFriend DJ, Robertson JFR, Blamey RW, Anderson L, Anderson E, et al. Pharmacokinetics, pharmacological and anti-tumour effects of the specific antiestrogen ICI 182780 in women with advanced breast cancer. *Br J Cancer* 1996;74:300-8.
- 18 Schwarzel WC, Kruggel WG, Brodie HJ. Studies on the mechanism of estrogen biosynthesis. VIII. The development of inhibitors of the enzyme system in human placenta. *Endocrinology* 1973;92:866-80.
- 19 Buzdar A, Jonat W, Howell A, Jones SE, Blomqvist C, Vogel CL, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *J Clin Oncol* 1996;14:2000-11.
- 20 Buzdar A, Jonat W, Howell A, Yin H, Lee D. Significant improved survival with Arimidex (anastrozole) versus megestrol acetate in postmenopausal advanced breast cancer: updated results of two randomized trials [abstract]. *Proc Am Soc Clin Oncol* 1997;16:156.
- 21 Smith I, Dombrowsky P, Falkson G, Leonard, R, Panasci L, Bellmunt J, et al. Double-blind trial in postmenopausal women with advanced breast cancer showing a dose-effect and superiority of 2.5 mg letrozole over megestrol acetate. *Eur J Cancer* 1996;32A(suppl 2):49.
- 22 Marty M, Gershanovich M, Campos B, Romien G, Lurie H, Bonaventura T, et al. Letrozole, a new potent, selective aromatase inhibitor superior to aminoglutethimide (AG) in postmenopausal women with advanced breast cancer previously treated with anti-oestrogens [abstract]. *Proc Am Soc Clin Oncol* 1997;16:156.
- 23 Bergh, J, Bonnetterre J, Houston SJ, Uiger HJ, Murray R, Nortier J, et al. Vorozole (Rivizor) versus aminoglutethimide (AG) in the treatment of postmenopausal breast cancer relapsing after tamoxifen [abstract]. *Proc Am Soc Clin Oncol* 1997;16:156.
- 24 Goss P, Winer E, Tannock I, Schwartz LH, Kremer AB for the North American Vorozole Study Group. Vorozole vs megestrol in postmenopausal patients with metastatic breast carcinoma who had relapsed following tamoxifen [abstract]. *Proc Am Soc Clin Oncol* 1997;16:155.
- 25 Dowsett M. Biological background to aromatase inhibition. *The Breast* 1996;5:196-201.
- 26 Coombes RC, Hughes SWM, Dowsett M. 4-Hydroxyandrostenedione: A new treatment for postmenopausal patients with breast cancer. *Eur J Cancer* 1992;28A:1941-5.
- 27 Di Salle E, Ornati G, Paridaens R, Coombes RC, Lobelle JP, Zurlo MG. Preclinical and clinical pharmacology of the aromatase inhibitor exemestane (FCE 24304). In: Motta M, Serio M, eds. *Sex hormones and antihormones in endocrine dependent pathology: basic and clinical aspects*. Amsterdam, Elsevier, 1994:303-9.
- 28 Dowsett M, Vorobioff DA, Kleeberg UR, Carrion RP, Dodwell DJ, Robertson JFR, et al. A randomized study assessing oestrogen suppression with arimidex (anastrozole) and formestane in postmenopausal advanced breast cancer patients. *Eur J Cancer* 1996;32A(suppl 2):49.
- 29 Howell A, Mackintosh J, Jones M, Redford J, Wagstaff J, Sellwood RA. The definition of the "no change" category in patients treated with endocrine therapy and chemotherapy for advanced carcinoma of the breast. *Eur J Cancer Clin Oncol* 1988;24:1567-72.

Endpiece

Misleading appearances

A woman accompanied her husband to the doctor and waited for him during his checkup. After the examination the doctor came out and said, "I don't like the way your husband looks." "Neither do I," said the woman, "but he's good with the kids."

From *The Best of Medical Humour* (Howard J Bennett, ed. Philadelphia: Hanley and Belfus, 1997)