The Breast (1996) 5, 192–195

ESO TASK FORCE ARTICLE

Clinical studies with the specific 'pure' antioestrogen ICI 182780

A. Howell, D. J. DeFriend*, J. F. R. Robertson†, R. W. Blamey†, L. Anderson, E. Anderson‡, F. A. Sutcliffe§ and P. Walton§

*CRC Department of Medical Oncology, University of Manchester, *Department of Surgery, University Hospital of South Manchester, †Department of Surgery, City Hospital, Nottingham, §Zeneca Pharmaceuticals, Macclesfield, ‡Tumour Biochemistry Laboratory, Christie Hospital, Manchester, UK*

S U M M A R Y. We have shown that ICI 182780 inhibits the growth of metastatic tumour cells derived from patients failing treatment with tamoxifen when grown in vitro. In this system tamoxifen stimulates growth of tumour cells which can be reversed by addition of ICI 182780 to tamoxifen in culture. In a phase I study we have demonstrated that treatment of patients for 7 days before surgical excision of the tumour resulted in marked down regulation of ER, inhibition of growth and oestrogen-induced gene expression. More recently we demonstrated that treatment of advanced breast cancer patients with ICI 182780, after tamoxifen failure, resulted in a high remission rate and prolonged periods of remission with very few side-effects. These data indicate that further clinical trials of ICI 182780 are warranted. We expect that it will show superiority over conventional endocrine therapy.

DISCUSSION

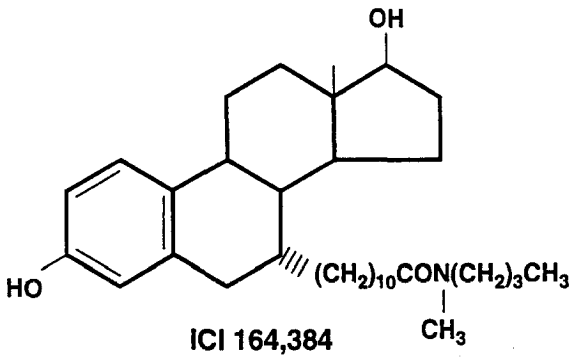
Tamoxifen was first used in the clinic in December 1969.[1] It rapidly became the endocrine therapy of choice for women with advanced breast cancer because, although no more active than endocrine therapies used at that time, it had fewer side effects. This feature together with beneficial agonist effects on bone and lipids has lead to its widespread use as adjuvant therapy after surgery for primary breast cancer and in clinical trial as a preventative agent in women at high risk. However, there is strong evidence derived from experiments with human mammary tumour cells grown in vitro as reported by Nicholson et al[2] in this issue and in nude mice[3] that tamoxifen may become an agonist with respect to tumour cells. Tumour agonism is also seen in the clinic, although uncommon, since withdrawal responses to tamoxifen have clearly been demonstrated.[4] Tumour regression after withdrawal of tamoxifen clearly suggests that, at the time of progression, tamoxifen was stimulating tumour growth and that response is due to removal of the 'oestrogenic' stimulus.

In the mid-1980s scientists at Zeneca Pharmaceuticals (then ICI) considered that the development of oestrogen antagonists without agonist activity – 'pure' or specific antioestrogens – might be of benefit clinically for control of hormone-dependent tumours and hormone-induced benign conditions such as endometriosis and benign breast disease. They might also provide more specific probes for understanding molecular mechanisms of hormone-receptor interactions.

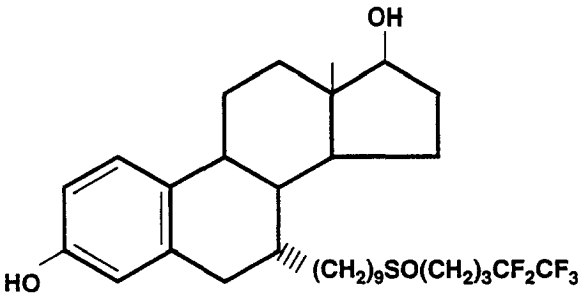
It was felt that synthesis of further triphenylethylene analogues of tamoxifen would not produce structures with suitable pharmacological profiles and a novel chemical approach was necessary. The work of Baulieu's group[5] identified the C7-position of oestradiol as a point of attachment for long alkyl substituents which could produce specific antagonists without reducing the affinity of molecules for the oestrogen receptor (ER).

A series of C7 analogues was tested in the immature rat uterus assay,[6] the model which provides the simplest demonstration of a difference between partial agonists and specific antagonist antioestrogens. In the absence of oestradiol, tamoxifen is a partial agonist and stimulates growth of the uterus. However, in the presence of oestrogens, tamoxifen partially reverses oestrogen-induced growth. Most of the non-steroidal antioestrogens in the clinic (i.e. tamoxifen, toremifene, raloxifene, droloxifene, TAT-59 and idoxifene) have more or less agonist and antagonist activity in this assay. The specific antioestrogens ICI 164384 and ICI 182780 (Fig. 1) act as complete antagonists of oestrogen

Address correspondence to: A. Howell, CRC Department of Medical Oncology, University of Manchester, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, UK



ICI 164,384



ICI 182,780

Fig. 1 Structures of the steroidal 'pure' antioestrogens ICI 164384 and ICI 182780.

action and have no agonist activity in the absence of oestrogen in the uterus assay.[7] ICI 182780 was selected to enter the clinic as it has higher affinity for ER (equal to oestradiol) than the first lead compound (ICI 164384).

The first clinical trial short-term administration of ICI 182780 by daily administration before surgery for breast cancer is outlined by Anderson et al.[8] There was very little toxicity from daily injections of ICI 182780 and even after short-term administration there was marked downregulation of ER and progesterone receptor (PR) and inhibition of proliferation. Thus, it was clear that ICI 182780 had antitumour effects in humans and the question then arose regarding the best clinical scenario to test for tumour regression. It was not clear that the compound should continue in development and a trial was required which would give the indication of maximal compound potency whilst requiring as few patients in trial as possible.

As ICI 182780 had been shown to inhibit the proliferation of tamoxifen-resistant human mammary tumour cell lines when grown in vitro or in nude mice, it was decided to test the compound in women with advanced breast cancer who had failed tamoxifen therapy given either as an adjuvant at initial diagnosis or given for advanced disease. Because there was no guarantee of response, and it was an unusual study of sequential use of two antioestrogens, we selected patients likely to respond to therapy. They had to have failed on adjuvant tamoxifen given for 2 or more years, or, when given for advanced disease the patients must have had a complete or partial reponse to tamoxifen, or remained stable, for at least 6 months. Nineteen patients matched these criteria and were recruited in Manchester and Nottingham between 11 November 1992 and 2 June 1993.

Before beginning the trial we wished to determine whether 'primary' human tumours were stimulated by tamoxifen in a colony assay and, if so, whether such stimulation could be reversed by the addition of ICI 182780. Tumour cells from six pleural effusions in patients failing tamoxifen were plated in semi-solid agar without serum oestradiol or phenol red. Growth in four of the six was significantly stimulated by 10^{-10} M oestradial and in two by 10^{-8} M 4-hydroxytamoxifen (Fig. 2).[9] Both the oestradiol and tamoxifen stimulation could be reversed by the addition of 10^{-8} M ICI 182780. These data confirm that some primary tumours may be stimulated in vitro by tamoxifen at the time of clinical progression on the drug. The fact that stimulation could be reversed by ICI 182780 gave us confidence to initiate a clinical trial.

At the time of these studies ICI 182780 was not considered to be bioavailable in an oral form so a depot injection was developed by dissolving the drug in a castor oil-based vehicle. As judged by inhibition of uterine proliferation in adult female monkeys it was predicted that serum levels in excess of 2–3 μg/ml would be sufficient to produce a therapeutic effect in patients with advanced breast cancer.[10] It was found that levels of ICI 182780, using a 250 mg depot, reached a peak of 7.5 ng/ml during the first 8 days of treatment and at 28 days there was still a mean of 3 ng/ml. During the sixth monthly cycle there was evidence of accumulation of the drug such that the level at 28 days had a mean of 6 ng/ml. Thus, levels above the minimum therapeutic levels were attained.

Full details of the study will be published shortly.[1] However, in summary, of the 19 patients treated, 7 (37%) had a partial response and a further 6 (32%) stabilization of their disease for more than 6 months. The median duration of response has just been reached and is 25 months. Five patients remain in remission for 30+, 30+, 32+, 33+ and 33+ months respectively. When we looked at a matched group of women from our database with the same favourable characteristics, treated with megestrol acetate, the response rate was 60% (PR + no change) but the median duration of remission was only 14 months. Thus, not only do patients respond to steroidal antioestrogen after failure on a non-steroidal compound (tamoxifen) but the duration of response appears twice as long. These conclusions are, of course, tentative and will need confirmation in further clinical trials. It is of interest that treatment of MCF-7 tumours in nude

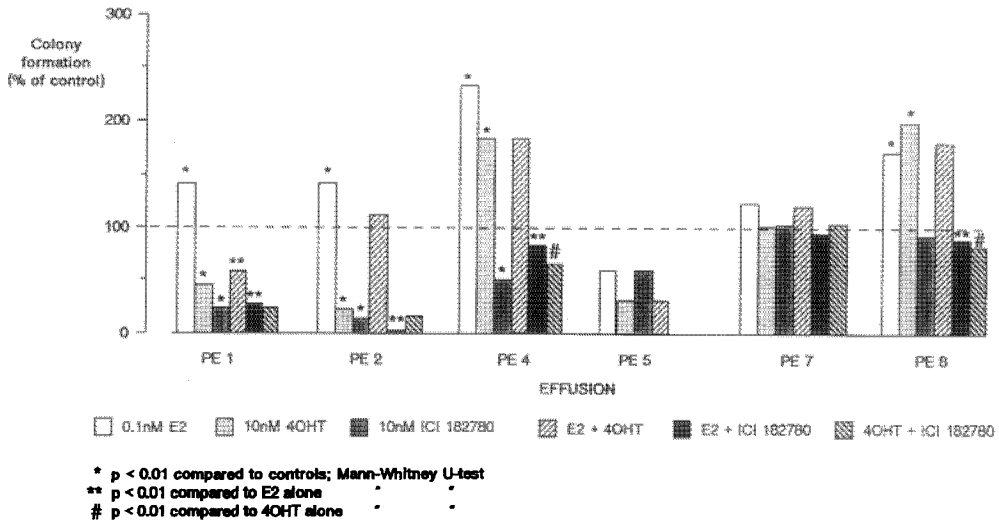


Fig. 2 Responses of cancer cells from 6 clonogenic pleural effusions to oestradiol (E2), 4-hydroxytamoxifen (4 OHT) and ICI 182780. Columns show CFE's as percentages of the control CFE for each effusion. Reproduced by the kind permission of Stockton Press from DeFriend et al. Br J Cancer 1994; 70: 204–211.

mice with ICI 182780 produced tumour control for twice as long as tamoxifen, as reported by Osborne.[3]

There have been no major side effects with ICI 182780 up to the maximum treatment period to date (November 1995) of 33 months. In view of the degree of oestrogen suppression, as judged by very low or undetectable ER levels shown in the tumours of women in the phase I study, we anticipated inducing hot flushes and hot sweats. However, if hot flushes were present prior to the trial they were not increased and none were induced. LH and FSH levels were initially low for postmenopausal women, presumably related to treatment with tamoxifen. During treatment both hormones rose to levels in the middle of our normal range and not the high levels expected if all effects of oestrogen were removed from the hypothalamus and pituitary gland.[11] The apparent lack of effect of ICI 182780 on the hypothalamus suggests that the molecule might not pass the blood brain barrier.

In rats oestrogen not only controls gonadotrophin secretion during the menstrual cycle but also reduces food intake and decreases body weight. Tamoxifen has a similar effect to oestrogens but there was no change of food intake with ICI 164384, ICI 182780 and a specific non-steroidal antioestrogen ZM 189154.[12] Again these data support the suggestion that the specific antioestrogens fail to penetrate the blood brain barrier. The selective action of ICI 182780 was confirmed by Wade et al[13] who demonstrated that [3H] oestradiol uptake in the rat was blocked by tamoxifen in all target tissues including the brain but treatment with ICI 182780 failed to block uptake at this site. Experiments in vitro with brain-derived ER showed tight binding of ICI 182780 further suggesting that lack of binding in vivo was related to inability of the molecule to cross the blood brain barrier.

We expected to find patients complaining of vaginal dryness during treatment with ICI 182780 but again, surprisingly, this was not reported by any of the 19 patients, even after prolonged treatment periods. Serial uterine ultrasound measurements were performed in five patients. All had endometrial 'thickening' compatible with a partial agonist effect produced by previous treatment with tamoxifen but there was no increase on treatment with ICI 182780 over periods of up to 15 months. We expected to detect a decline in endometrial thickness but were reassured there was no further increase suggesting an antioestrogenic effect of ICl 182780 on the uterus. The stabilizing effect on the endometrium was seen also in short-term studies where ICI 182780 was given for 7 days before hysterectomy in premenopausal women[14] and after longer term administration in adult female monkeys.[10]

Sex hormone binding globulin (SHBG) levels tended to be high at the beginning of treatment and declined during therapy with ICI 182780. Serum cholesterol, triglycerides and high and low density lipoprotein cholesterol were unchanged with up to 15 weeks of treatment with ICI 182780.[11] The SHBG and lipid data are difficult to interpret. A fall in SHBG suggests that this was due to either removal of the oestrogenic effect of tamoxifen or an antioestrogen effect of ICI 182780 on the liver. If the latter, serum lipid levels should have risen but they remained stable throughout the period of study. Further work is necessary to delineate the effect of ICI 182780 on the human liver.

One of the major concerns regarding a new antioestrogen in women is the potential for a negative effect on bone. As patients in the phase II study had advanced breast cancer, bone density measurements were not made. Initial observation in normal adult female rats showed that ICI 182780 had no effect on bone whilst showing the expected inhibitory effect on the uterus.[15] However, more recent histomorphometric studies have demonstrated an oophorectomy-like action of ICI 182780 on tibial cancellous bone volume in intact rats.[16] In this study a 20% reduction in cancellous bone volume was reported. The reason for the discrepancy between the two studies is not clear. It will be important to perform careful bone density studies in future trials of ICI 182780. It is possible that in humans ICI 182780 will be peripherally selective with respect to bone at the final dose used. Recent studies with a specific ('pure') non-steroidal antioestrogen in immature rats showed no effect on bone at doses which produced maximal uterine atrophy; whereas five times the dose reduced bone density, although to a lesser extent than oophorectomy.[12]

Acknowledgement

The European School of Oncology gratefully acknowledges an educational grant from Zeneca Pharmaceuticals which made the meeting possible.

References

1. Cole M P, Jones C T A, Todd I D H. A new antioestrogenic agent in late breast cancer: an early clinical appraisal of ICI 146474. Br J Cancer 1971; 25: 270–275.
2. Nicholson R I, Francis A B, Kyme S, Gee J M W. Properties and mode of action of pure antioestrogen in breast cancer in vitro. The Breast 1996; 5: 00–00.
3. Osborne C K. Athymic nude mouse model for the study of new antioestrogens in breast cancer. The Breast 1996; 5: 00–00.
4. Howell A, Dodwell D, Anderson H, Redford J. Response after withdrawal of tamoxifen and progestogens in advanced breast cancer. Ann Oncol 1992; 3: 611–617.
5. Bucout R, Vignau M, Torelli V et al. New biospecific adsorbents for the purification of oestradiol receptor. J Biol Chem 1978; 253: 8221–8228.
6. Harper M J K, Walpole A L A new derivative of triphenylethylene: effect on implantation and mode of action in rats. J Reprod Fertil 1967; 13: 101–119.
7. Wakeling A E, Dukes M, Bowler J A. Potent specific pure antioestrogen with clincal potential. Cancer Res 1991; 51: 3867–3873.
8. Anderson E, Nicholson R, Dowsett M, Howell A. Models of new antioestrogen in vivo: primary tumours. The Breast 1996; 5: 00–00.
9. De Friend D, Anderson E, Bell J, Wilks D P, West C M L, Howell A. Effects of 4-hydroxytamoxifen and a novel pure antioestrogen (ICI 182780) on the clonogenic growth of human breast cancer cells in vitro. Br J Cancer 1994; 70: 204–211.
10. Dukes M, Waterton J C, Wakeling A E. Antiuterotrophic effects of the pure antioestrogen ICI 182780 in adult female monkeys (*Macaca-nemestrina*): quantitive magnetic resonance imaging. J Endocrinol 1993; 138: 203–210.
11. Howell A, DeFriend D J, Robertson J F R et al. Pharmacokinetics, systemic and antitumour effects of the specific antioestrogen ICI 182780 in women with advanced breast cancer. Br J Cancer, 1996. In press.
12. Dukes M, Chester R, Yarwood L, Wakeling A E. Effects of non-steroidal pure antioestrogen, ZM 189154 on oestrogen target organs of the rat including bones. J Endocrinol 1994; 141: 335–341.
13. Wade G N, Blaustein J D, Gray J M, Meredith J M. ICI 182780: a pure antioestrogen that affects behaviours and energy balance in rats without acting in the brain. Am J Physiol 1993; 265: R1392–R1398.
14. Thomas E J, Thomas N M, Walton P L, Dowsett M. The effects of ICI 182780, a pure antioestrogen, on reproductive endocrinology in normal, pre-menopausal women. J Endocrinol 1993; 137s: 183.
15. Wakeling A E. The future of new pure antioestrogens in clinical breast cancer. Breast Cancer Res Treat 1993; 25: 1–9.
16. Gallagher A, Chambers T J, Tobias J H. The estrogen antagonist ICI 182780 reduces cancellous bone volume in female rats. Endocrinology 1993; 133: 2787–2791.