

References

- Davis LG, Weber DJ, Lemon SM. Horizontal transmission of hepatitis B virus. *Lancet* 1989; i: 889-93.
- Bernier RH, Sampliner R, Gerety R, Tabor E, Hamilton F, Nathanson N. Hepatitis B infection in households of chronic carriers of hepatitis B surface antigen: factors associated with prevalence of infection. *Am J Epidemiol* 1982; 116: 199-211.
- Franks A, Berg CJ, Kane MA, et al. Hepatitis B virus infection among children born in the United States to Southeast Asian refugees. *N Engl J Med* 1989; 321: 1301-05.
- Friede A, Harris JR, Kobayashi JM, Shaw FE, Schoemaker-Nawas PC, Kane M. Transmission of hepatitis B virus from adopted Asian children to their families. *Am J Public Health* 1988; 78: 26-29.
- van Ditzhuysen Th JM, De Witte-van Der Schoot E, van Loon AM, Rijntjes PJM, Yap SH. Hepatitis B in an institution for the mentally retarded. *Am J Epidemiol* 1988; 128: 629-38.
- Hayashi J, Kashiwagi S, Nomura H, Kajiyama W, Ikematsu H. Hepatitis B virus transmission in nursery schools. *Am J Epidemiol* 1987; 125: 492-98.
- Van Damme P, Meheus A. Hepatitis B in mental handicap hospitals. *Lancet* 1989; i: 840-41.
- McPhillips JC, Collins JC, Spigland I. Hepatitis B virus infections transmitted from retarded children to their families during brief home exposure. *J Pediatr Gastroenterol Nutr* 1984; 3: 69-71.
- Jenison SA, Leman SM, Baker LN, Newbold JE. Quantitative analysis of hepatitis B virus DNA in saliva and semen of chronically infected homosexual men. *J Infect Dis* 1987; 156: 299-307.
- Cancio-Bello TP, de Medina M, Shorey J, Valledor MD, Schiff ER. An institutional outbreak of hepatitis B related to a human biting carrier. *J Infect Dis* 1982; 146: 652-56.

Department of Epidemiology and Community Medicine, University of Antwerp, 2610 Antwerpen, Belgium (P Van Damme MD, M Cramm MD, J-C Van Der Auwera, A Meheus PhD); and Institute of Hygiene and Epidemiology, Brussels, Belgium (R Vranckx PhD)

Correspondence to: Dr Pierre Van Damme

Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer

Anthony Howell, David DeFriend, John Robertson, Roger Blamey, Peter Walton

We treated 19 patients with advanced breast cancer resistant to tamoxifen with a new specific antioestrogen (ICI 182780) which, in animal studies, has no agonist activity. 13 (69%) patients responded (7 had partial responses and 6 showed no change) to monthly intramuscular injections of ICI 182780 after progression on tamoxifen, for a median duration of 18 months with minimum side effects. Preliminary evidence suggests that the agent is without effects on the liver or the hypothalamic-pituitary axis. ICI 182780 appears to be a promising new agent for treatment of advanced and early breast cancer.

Lancet 1995; 345: 29-30

Although half of all patients with advanced breast cancer have cancers which either regress or remain stable when treated with tamoxifen, tumours eventually become resistant after a median duration of remission of fifteen months. Although an antagonist with respect to the cancer, tamoxifen is an oestrogenic agonist with respect to bone, liver, and endometrium. One cause of resistance may be the cancer reacting to tamoxifen as an agonist or that tamoxifen is, in some way, rendered unavailable to oestrogen receptors so that endogenous oestradiol is able to restimulate cancer growth. To test this hypothesis, we treated patients with cancers resistant to tamoxifen with an antioestrogen (ICI 182780: 7 α -[9(4,4,5,5,5 pentafluoropentylsulfinyl)nonyl]oestra-1,3,5,(10)-triene-3,17 β -diol) which, in animal studies, has been shown to have no agonist activity.¹

ICI 182780 is a steroidal antioestrogen with an alkylsulphonyl side chain in the 7 α position. There is evidence that the side chain prevents dimerisation of two molecules of the oestrogen receptor which is a prerequisite for gene transcription.² In contrast, tamoxifen, like oestrogens, causes receptor dimerisation

19 postmenopausal patients less than 81 years old with advanced, histologically verified, breast cancer resistant to tamoxifen were treated with ICI 182780. The study was approved by the ethics committees of each clinical centre. Patients were included if they had been treated with tamoxifen as an adjuvant to surgery for more than two years and then relapsed or treated with tamoxifen for advanced disease, had a complete or partial remission, or no change for at least six months⁴ and subsequently progressed. Patients were excluded if they had serious intercurrent disease, a WHO performance status of greater than 2 and a life expectancy of less than 3 months, or had received other chemotherapy. One patient had adjuvant therapy for only 9 months and progressed, and was thus a protocol violation but is included in the analysis. She had progressive disease when treated with ICI 182780. The predominant sites of disease at the time of relapse on tamoxifen were: breast/chest wall (7), lymph nodes (1), bone (9), and lung/pleura (2). After giving informed consent, all patients underwent baseline staging investigations before starting treatment with ICI 182780; including radiographs, liver ultrasound or computed tomograph scan (all every 1-2 months), and isotope bone scan (every 6 months). ICI 182780 was administered as a long-acting formulation in a castor oil-based vehicle by monthly intramuscular injection into a buttock. For safety appraisal, the first 4 patients received escalating doses of ICI 182780, starting with 100 mg the first month and increasing to 250 mg from month 2 onwards, following confirmation of lack of local or systemic drug toxicity at the 100 mg dose. Patients 5-19 received 250 mg/month from the outset. Treatment with ICI 182780 was continued until cancer progression occurred. Patients were seen every 3-7 days during the first month to monitor local and systemic drug tolerability and to collect blood samples for pharmacokinetic studies. Thereafter, review was done monthly to evaluate response and to monitor local and systemic drug tolerability. Blood samples were taken before treatment and at monthly intervals thereafter for measurement of full blood count, biochemistry, serum hormones, and lipids. Cancer response was evaluated according to UICC criteria. To qualify for the "no change" category, cancer growth had to stabilise for more than six months.⁴

| Response to ICI 182780 | Number (%) | Duration (months) |
|------------------------|------------|--|
| Partial | 7 (37) | 20+(PR 19), 18+(NC 8), 17+(A67), 17 (PR24) 12 (A74), 8 (A20), 3 (A77) |
| No change | 6 (32) | 23+(NC8), 18+(A74), 18+(A71), 16+(NC 48), 16+(A23), 9 (NC 34) |
| Progression | 6 (31) | All patients progressed in <8 weeks. Previous treatment with tamoxifen A48, A45, NC 7, PR 8, 9, NC12 |

Letters in brackets indicate response to tamoxifen when given for advanced disease (PR=partial remission, NC=no change, PD=progressive disease) or if given as an adjuvant therapy (A). Numbers in brackets indicate duration of treatment with

All 19 patients were evaluable (table). 13 (69%) responded to treatment for a median duration of more than 18 months. 9 are still responding and continuing treatment with ICI 182780 after 16–23 months. Sites of response were soft tissue (4), bone (7), and lung (3). Responses were seen in 6 of 9 women who had progressed whilst receiving tamoxifen for advanced disease and in 7 of 10 women who had received tamoxifen as adjuvant therapy. There appeared to be no association between duration of treatment with tamoxifen and subsequent response to ICI 182780. No serious drug-related adverse events occurred; minor adverse events were reported by 2 patients—transient blood-stained vaginal discharge and a subjective feeling of living in a “dream like state” (similar to that she had whilst taking tamoxifen) in one patient, and alteration of body odour (noticed by her husband for one month), possibly associated with increased hair greasiness, in the other. There was no alteration in the frequency of night sweats or hot flushes, if already present, and none were initiated. None of the patients reported vaginal dryness or altered libido on direct questioning at each out-patient attendance. ICI 182780 appeared well tolerated at the site of injection despite the relatively large 5 mL volume administered, with only 3 patients developing bruising or erythema on one occasion each. There were no clinically significant changes in full blood count or unexpected changes in biochemical tests.

Our study shows that patients with advanced breast cancer respond to a specific antioestrogen after failure of treatment with a partial-agonist antioestrogen. There appeared to be no cross resistance between ICI 182780 and tamoxifen in 69% of patients, whereas studies where tamoxifen-resistant patients were treated with another triphenylethylene antioestrogen, toremifene, have reported much higher rates of cross resistance.⁵ The median duration of response to ICI 182780 has not yet been reached, but is already longer than we might expect from other second-line endocrine therapies such as megestrol acetate.

ICI 182780 is thought to act exclusively as an antioestrogen via the oestrogen receptor.¹ Thus response to treatment with ICI 182780 suggests that oestrogen receptors remain functional and that tamoxifen therapy fails because cancer regrowth is produced by an oestrogenic stimulus. The cancer may acquire the capacity to respond to the partial agonist activity of tamoxifen and/or its various metabolites. This is supported by the ability of tamoxifen to stimulate proliferation of primary human breast cancer cells grown in-vitro,⁶ and also by the occasional clinical findings of patients whose cancers respond to withdrawal of tamoxifen at the time of treatment failure.⁷ Alternatively, changes in the intracellular handling of tamoxifen may reduce its ability to block oestrogen receptors and allow stimulation of cancer growth by endogenous oestrogens. This might occur as a result of cancer cells acquiring the ability to inactivate tamoxifen by intracellular degradation, intracellular sequestration to proteins other than oestrogen receptors, or by increased drug exclusion from the cell.^{8,9} Our data do not distinguish between these resistance mechanisms.

Preliminary data (not shown) from this study show an initial rise in serum gonadotropin during the first three

alteration of hot flushes and hot sweats seen in the study, these data suggest that, as was predicted from animal studies,¹ ICI 182780 may be without effect on the hypothalamus and pituitary gland. ICI 182780 may also be peripherally selective with respect to the liver since no significant effects on sex-hormone-binding globulin and lipid have been seen in the present study. In primates and in short-term studies in women,¹⁰ ICI 182780 inhibited endometrial proliferation at similar serum concentrations to those seen in this study. If a similar inhibitory effect of ICI 182780 were shown in longer-term studies, this would be a further therapeutic advantage of the specific antioestrogen, since tamoxifen is known to be associated with proliferation and endometrial cancer.⁵

Our study suggests that ICI 182780 may improve the rate and duration of response when used as a first-line treatment for advanced breast cancer, since it has no demonstrable agonist activity. Furthermore, the lack of toxicity or effect on serum lipids identify ICI 182780 as a candidate agent with which to investigate the potential benefits of specific antioestrogens in the adjuvant setting.

We thank Sisters Julie Kiernan and Nicki Scott for services in the clinical study; Mr E Hoare, Mr J M T Howat, and Mr R J Williams for referring patients; Jean Miller for help with preparing the manuscript; and Zeneca Pharmaceuticals for financial support.

References

- 1 Wakeling AE, Dukes M, Bowler J. A potent specific pure antioestrogen with clinical potential. *Cancer Res* 1991; 51: 3867–73.
- 2 Fawell SE, White R, Hoare S, Sydenham M, Page M, Parker MG. Inhibition of oestrogen receptor-DNA binding by the “pure” antioestrogen ICI 164,384 appears to be mediated by impaired receptor dimerization. *Proc Natl Acad Sci USA* 1990; 87: 6883–87.
- 3 Berry M, Metzger D, Chambon P. Role of the two activating domains on the oestrogen receptor in the cell-type and promoter-context dependent agonist activity of the anti-oestrogen 4-hydroxytamoxifen. *EMBO J* 1990; 9: 2811–18.
- 4 Howell A, Macintosh 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.
- 5 Vogel CL, Shemano I, Schonfelder J, Gams RA, Green MR. Multicenter phase II efficacy trial of toremifene in tamoxifen-refractory patients with advanced breast cancer. *J Clin Oncol* 1993; 11: 345–50.
- 6 DeFriend DJ, Anderson E, Bell J, Wilks DP, West CML, Howell A. Effects of 4-hydroxytamoxifen and a pure antioestrogen (ICI 182780) on the clonogenic growth of human breast cancer cells in vitro. *Br J Cancer* 1994; 70: 204–11.
- 7 Howell A, Dodwell DJ, Anderson H, Redford J. Response after withdrawal of tamoxifen and progestogens in advanced breast cancer. *Ann Oncol* 1992; 3: 611–17.
- 8 Osborne CK, Coronado E, Allred DC, et al. Acquired tamoxifen resistance: correlation with reduced breast tumor levels of tamoxifen and isomerization of trans-4-hydroxytamoxifen. *J Natl Cancer Inst* 1991; 83: 1477–82.
- 9 Pavlik EJ, Nelson K, Srinivasan S, et al. Resistance to tamoxifen with persisting sensitivity to estrogen: possible mediation by excessive antioestrogen binding site activity. *Cancer Res* 1992; 52: 4106–12.
- 10 Thomas EJ, Walton PL, Thomas NM, Dowsett M. The effects of ICI 182780, a pure antioestrogen, on the hypothalamic-pituitary-gonadal axis and on endometrial proliferation in premenopausal women. *Hum Reprod* 1994; 9: (in press).

CRC Department of Medical Oncology, University of Manchester, Christie Hospital, Manchester M20 9BX, UK (A Howell FRCP); Department of Surgery, University Hospital of South Manchester, Manchester, UK (D J DeFriend FRCS); Department of Surgery, City Hospital, Nottingham (Prof R W Blamey FRCS, J F Robertson FRCS); and Zeneca Pharmaceuticals, Macclesfield