VOL. 24, NO. 1, 1992

CODEN BCTRD6
ISSN 0167-6806

Breast Cancer Research and Treatment

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Kluwer Academic Publishers

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Breast Cancer Research and Treatment is published monthly (1992).
Subscription prices for 1992, Volumes 21, 22, 23 and 24 (3 issues each) are:
For institutions Dfl. 960,00/US$490.00 including postage and handling.
For individuals Dfl. 455,00/US$245.00 including postage and handling.
Subscriptions should be sent to *Kluwer Academic Publishers Group, P.O. Box 322, 3300 AH Dordrecht, The Netherlands,* or at, *P.O. Box 358, Accord Station, Hingham, MA 02018-0358, U.S.A.,* or to any subscription agent. Private subscriptions should be sent direct to the publishers. Changes of mailing address should be notified together with our latest label.
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ISSN 0167–6806

Printed in The Netherlands

Breast Cancer Research and Treatment **25**: 1–9, 1993.

15th San Antonio Breast Cancer Symposium — Plenary lecture

The future of new pure antiestrogens in clinical breast cancer

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Key words: breast cancer, antiestrogens, tamoxifen, resistance

Summary

The rationale for seeking to identify new pure antiestrogens was based on the recognition that existing antiestrogens, exemplified by tamoxifen, all possess partial agonist (estrogenic) activity. Conceptually, pure antiestrogens should be more effective than tamoxifen in ablating the mitogenic action of estrogens on breast tumor growth. The discovery and properties of the pure antiestrogens ICI 164,384 and ICI 182,780 are described and contrasted with those of tamoxifen. Key characteristics of these compounds which may be of particular relevance to their therapeutic application in the treatment of breast cancer are described. These include experimental data which predict efficacy in patients whose disease recurs during tamoxifen treatment, and the potential for pure antiestrogens to demonstrate greater efficacy than tamoxifen in first-line treatment of advanced breast cancer. The data imply that gains in efficacy could emerge as more rapid, more complete, or longer-lasting tumor remissions. Clinical trials with ICI 182,780 will reveal whether one or more of these predictions is correct.

Introduction

The nonsteroidal antiestrogen tamoxifen, ('Nolvadex'[1], ICI 46,474), is established as the treatment of choice for the endocrine therapy of advanced breast cancer [1]. Its ease of use and the absence of serious side effects in patients stimulated trials to assess the value of tamoxifen in adjuvant treatment of primary breast cancer [2,3] and, more recently, the initiation of trials to test its potential as a chemo-preventive agent in women at high risk of developing breast cancer [4,5]. The proportion of patients with advanced breast cancer who respond to Nolvadex, and the average duration of response, are not significantly greater than those obtained with other endocrine treatments. Nolvadex treatment is palliative, and the majority of women who respond to treatment will experience relapse. In adjuvant therapy, Nolvadex extends the disease-free interval and overall survival compared with no treatment [3]. Current clinical practice in the adjuvant use of Nolvadex shows an increasing trend towards continuation of drug treatment until disease recurrence. These clinical observations pose several important questions about future directions for treatment,

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two of which are considered here. Firstly, what treatment(s) should be applied in patients relapsing during or after Nolvadex treatment? Secondly, will pure antiestrogens provide more effective treatment of advanced breast cancer than Nolvadex or other currently available drug treatments? It will be argued that pure antiestrogens have particular properties which will provide answers to these important questions.

Rationale for pure antiestrogens

In early animal studies it was shown that tamoxifen antagonises the tropic actions of endogenous or exogenous estrogens but also, when administered alone to immature (or ovariectomised) rats and mice, itself has tropic (estrogenic) effects [6,7]. Thus, tamoxifen has the characteristics of an antiestrogen with partial agonist activity. In animals and in man the balance between stimulatory and inhibitory activities of tamoxifen varies widely depending on the organ, cell, or specific protein measured as an indicator of estrogenic activity [8,9]. Tamoxifen shares this property with chemically similar, triphenylethylene-derived agents, described earlier and more recently [10]. A consequence of this partial agonist activity is that *complete* blockade of the action of estrogens cannot be achieved with tamoxifen. Although it is not known whether the partial agonist activity of tamoxifen in any way limits its clinical efficacy, *complete* ablation of the estrogen-mediated tumor growth is a desirable objective since it might be anticipated to provide more rapid, more complete, or longer-lasting tumor responses. Conceptually, this objective could be achieved by treatment with a pure antiestrogen.

The profile of activity of a pure antiestrogen is easily understood in the pharmacological sense; developments in understanding the molecular mode of action of estrogens and how this is affected by tamoxifen, also facilitated a biochemical concept of how such agents might work.

Estrogens stimulate tumor growth by binding to estrogen receptors (ER) in the cell nucleus. The estrogen-ER complex then dimerizes and binds to specific DNA sequences (estrogen response elements, ERE), to activate the transcription of estrogen responsive genes which ultimately trigger cell proliferation. Tamoxifen disrupts this process by binding to ER and interfering with normal transcriptional responses to estrogens [11]. The estrogenic effects of tamoxifen strongly imply that the tamoxifen-receptor complex in the cell nucleus is not inert — it retains some capacity to transduce signals similar to those induced by the estrogen-ER complex [11]. In contrast it might be anticipated that pure antiestrogens should bind to ER to form an ER-complex which either does not bind to ERE's or, if DNA binding does occur, is unable to promote transcription.

Discovery of novel antiestrogens

The two key elements of the search for pure antiestrogens were, firstly, a medicinal chemistry strategy to identify novel ER ligands and, secondly, robust and reliable biological test systems. The strategy chosen for initial chemistry is described elsewhere [12] and involved synthesis of estradiol analogues bearing C7-substituents which retain a high affinity for ER, an essential feature recognized in our drug target profile [13]. Facile and reproducible testing for both estrogen agonist and antagonist activity *in vivo* was provided by measurement of uterotropic and antiuterotropic effects in immature rats [14]. In this assay, tamoxifen alone maximally increases the uterine weight 2-fold, compared with 5-fold for estradiol. Correspondingly, coadministration of tamoxifen and estradiol demonstrates a maximum 60% inhibition of the tropic action of estradiol. In addition to this bioassay, the intrinsic potency of new compounds could be monitored accurately *in vitro* by receptor binding measurements [15] and

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