Idoxifene: Report of a Phase I Study in Patients with Metastatic Breast Cancer

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ABSTRACT

Idoxifene, a novel antiestrogen with reduced estrogenic activity when compared to tamoxifen, has been given to 20 women with metastatic breast cancer, 19 of whom had received tamoxifen previously, in doses between 10—60 mg. Idoxifene had an initial half-life of 15 h and a terminal half-life of 23.3 days. At a maintenance dose of 20 mg, a mean steady-state level of 173.5 ng/ml was achieved. Significant falls in luteinizing hormone and follicle-stimulating hormone were seen, but the falls were not dose related. Idoxifene was well tolerated, with 11 patients complaining of mild symptoms similar to those seen with tamoxifen. Fourteen patients continued idoxifene therapy for 1—56 weeks; 4 patients showed stabilization of disease for 6—56 weeks and 2 patients showed a partial response.

INTRODUCTION

The use of the antiestrogen tamoxifen is well established in the treatment of breast cancer in patients with advanced disease and as adjuvant therapy. However, tamoxifen has a number of serious drawbacks including: (a) the fact that only a proportion of breast cancers respond for a limited time point; and (b) tamoxifen possesses estrogenic properties that are probably responsible for the increased incidence of endometrial cancer observed during tamoxifen therapy and can also lead to tumor "flare" (1). Many compounds have been synthesized in an attempt to overcome these problems, including LY117018 (2), MER-25 (3), toremifene (4), and ICI 182,780, the latter displaying properties of a pure antiestrogen (5).

Some of these compounds have potential side effects and problems. Thus, a pure antiestrogen such as ICI 182,780 might cause osteoporosis; in contrast, the estrogen agonist activity of tamoxifen actually causes an increase in bone density (6). LY117018 is rapidly conjugated, metabolized, and excreted (2), whereas MER-25 has low potency and is more toxic than tamoxifen (3).

Idoxifene was synthesized in an attempt to produce an antiestrogen with lower estrogenic but greater antiestrogenic activity than tamoxifen (7, 8). We reasoned that we could prevent the conversion by the liver of the dimethylamino group to give the desmethyl metabolite and release of formaldehyde with possible toxic side effects by substituting a pyrrolidino group at this position. Also, iodination of the molecule at the 4-position not only reduces estrogenic activity (9) but also blocks 4-hydroxylation and subsequent rapid glucuronidation as occurs with tamoxifen (10) and should give the compound a longer duration of action in vivo. This different metabolic handling of idoxifene compared to tamoxifen should also circumvent proposed resistance mechanisms with a metabolic boost (11). However, recent work using nonisomeric analogues of tamoxifen and metabolites has called into question the importance of such "metabolic" mechanisms of tamoxifen resistance (12, 13). Idoxifene showed 2.5- to 5-fold higher affinity for the ER3 compared with tamoxifen (8, 9) and was 1.5-fold more effective in causing inhibition of estrogen-induced growth of MCF-7 cells (9). In vivo idoxifene was more effective in causing tumor regression in the N-nitrosomethylurea-induced mammary carcinoma model system (9). In the immature rat and mouse uterotrophic assays, idoxifene possessed less agonist activity than tamoxifen and inhibited estrogen-induced vaginal cornification, whereas tamoxifen did not (9). Another potential advantage of idoxifene over tamoxifen is that it is a more potent antagonist of calmodulin function (14). Such antagonism has been proposed to play a significant role in the inhibition of breast cancer cell growth by tamoxifen (15, 16).

Metabolically, idoxifene has greater stability than tamoxifen, as indicated by a 2.5-fold lower rate of metabolism in isolated rat hepatocytes (17). This is reflected in vivo by an approximate doubling of the terminal half-life of idoxifene compared to tamoxifen in the rat (17).

Preclinical toxicology of idoxifene was carried out under the auspices of the Cancer Research Campaign Phase I Committee. A single-dose study in mice at 100 g/kg showed no mortality or behavioral change. Histology showed mild vacuolation of the interstitial cells in the ovary and mild dilation of uterine glands but no other abnormalities. A repeat-dose oral study in mice was then carried out which, at doses of 25—50 mg/kg given daily for 4 weeks, showed some mild reduction in weight, reduced uterine and ovarian weight, and ovarian interstitial hyperplasia. No other abnormality was seen.

Since the agonist activities of tamoxifen are reflected in reduced gonadotrophin levels and increased SHBG levels in postmenopausal women (18, 19), these endocrine parameters can be used as possible markers of the pharmacological/estrogenic effect of idoxifene. Thus, the opportunity was taken in this Phase I study to investigate the effects of varying doses of idoxifene on the plasma levels of these endocrine parameters.

In this study, we report the findings of a Phase I study in which we have investigated the pharmacokinetics and pharmacodynamics of idoxifene in 20 postmenopausal women with advanced breast cancer.

PATIENTS AND METHODS

Patients. Twenty patients who attended Charing Cross and Westminster Hospital breast clinics with advanced breast cancer entered the trial between July 1992 and January 1993. The mean age of the patients was 60 (range, 37—84). Ten patients had predominant skin or soft tissue disease, 6 had locally recurrent disease, and 7 had predominantly bone metastases. Five had nodal recurrence, two had lung metastases, and two had liver metastases.

Eligibility criteria included: histological proof of breast cancer; documented, measurable disease; postmenopausal status; previous endocrine therapy; ER positivity or unknown receptor status; adequate renal (blood urea no more than twice the upper limit of normal), hepatic (liver function tests no more than twice the upper limit of normal), and normal bone marrow function; and a life expectancy of more than 6 months. Patients had not received hormone therapy or chemotherapy within 4 weeks prior to starting idoxifene.
The median number of previous endocrine therapies was 2 (range, 1–4): 19 patients had received tamoxifen. Ten of these patients had responded to tamoxifen in the past, and 9 had either failed to respond or simply stabilized. Thirteen patients had received chemotherapy in the past. Details of previous tamoxifen in the past, and 9 had either failed to respond or simply stabilized.

Study Design. Single oral doses of idoxifene (10, 20, 40, and 60 mg) were administered to groups of 5 patients. After a 1-week interval, patients then received the same dose daily for 1 week. With ethical committee approval, some patients remained on a standard dose (20 mg) of idoxifene until disease progression. Idoxifene was synthesized by a modification of the published route (8) and formulated at the Cancer Research Campaign's Phase I/II Clinical Trials Committee Formulation Unit, University of Strathclyde, Glasgow, Scotland.

Assessment of Response Toxicity and Monitoring. At the start of the trial, patients were staged by means of clinical examination measurement of all measurable disease, routine hematology, biochemistry, chest X-ray and liver ultrasound, and bone scan or skeletal survey. Clinical examination and toxicity (using WHO criteria) were recorded on days 1, 2, 4, 6, 8, 9, 11, 13, and 14 and subsequently every 2 weeks.

Assessment of response was carried out using standard UICC criteria (20). Complete response (complete disappearance of all disease) for at least 4 weeks was described on a clinical basis, which included response as assessed radiologically or by physical examination. Partial response was defined as more than 50% tumor regression; stable disease was defined as showing less than 50% tumor regression or progression; progressive disease was defined as demonstrating more than 25% increase in measurable tumor parameters, i.e., by measurement of bidimensional diameters of measurable tumor nodules and metastases.

Hematology and biochemistry screen was carried out on days 1, 2, 8, 9, 11, 13, and 14 and then twice monthly. Clinical measurements were taken every 2 weeks. Full staging was repeated every 3 months for those patients who remained on treatment.

For endocrine assessment blood samples were taken for the measurement of E2, LH, FSH, and SHBG on days 0, 1, 2, 8, 9, 11, and 14 using previously described assays E2 (21); LH, FSH (22); and SHBG (23).

Pharmacokinetic Studies. Blood samples were taken prior to and at 2, 4, 8, and 12 h and 1, 2, 4, 6, and 8 days after a single oral dose of idoxifene (10–60 mg). On commencement of repeat daily dosing (day 8), further samples were taken prior to dosing on days 9, 11, 13, and 14 and then every 2–4 weeks from the patients continuing on treatment.

Measurement of Idoxifene. Samples of plasma (0.5 ml) were spiked with internal standard (4-iodotamoxifen) and mixed with acetonitrile (0.5 ml). The precipitated protein was removed by centrifugation (13,000 rpm for 2 min), and the supernatant was extracted twice with hexane:butanol (98:2; 5 ml). The combined extracts were evaporated to dryness at 40°C under nitrogen and reconstituted in eluent (200 μl); then aliquots (50–150 μl) were subjected to HPLC. Extraction efficiencies using this method were approximately 80%. The HPLC system comprised a Waters 680 gradient controller and two model 510 pumps (Millipore UK, Ltd., Watford, Herts, United Kingdom) fitted with a Spherisorb S3PC18 cartridge column (internal diameter, 15 cm x 4.6 mm; Phase Separations, Ltd., Deeside, Clywd, United Kingdom). The eluent consisted of methanol:water:diethylamine (83.5: 16.5:0.2), and the flow rate was 1.25 ml/min. Analytes were postcolumn converted to their highly fluorescent phenanthrene derivatives using a "Beam Boost" photochemical reaction unit (Technicon, Stockport, Cheshire, United Kingdom). Compounds were detected with a Perkin-Elmer LC-240 fluorescence detector using an EX (excitation wavelength) of 256 nm and an EM (emission wavelength) of 380 nm. Retention times and peak areas were recorded with a Trilab 3000 data system (Trivector Scientific, Beds, United Kingdom). The detection limit of the assay was 0.5 ng/ml for idoxifene.

RESULTS

Pharmacokinetics

After a single oral dose of idoxifene, peak plasma levels were reached after 2–8 h and then declined in a biphasic manner (Fig. 1). Following an initial distribution phase (half-life, 15 h) over the first 2–4 days, a very long elimination phase was apparent. Accurate determination of the terminal half-life was difficult due to there being little or no change in the plasma concentration of idoxifene over the final 48 h in many patients. Table 2 shows the mean pharmacokinetic parameters calculated at each dose level. Idoxifene demonstrated linear kinetics in the dose range studied, as indicated by linear relationships between dose and AUC0–192h (Fig. 2), Cmax, C24h, or C192h (P < 0.01 in all cases). These single-dose data gave a minimum

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**Table 1** The time interval between last treatment (in months) and response to a chemotherapy therapy.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Tamoxifen</th>
<th>Second line endocrine therapy</th>
<th>Chemotherapy*</th>
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<tr>
<td>1</td>
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<td>10 (PD)</td>
<td>9 (PD)</td>
</tr>
<tr>
<td>2</td>
<td>15 (NC)</td>
<td>14 (CR)</td>
<td>None</td>
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<tr>
<td>3</td>
<td>7 (PD)</td>
<td>5 (PD)</td>
<td>28 (PD)</td>
</tr>
<tr>
<td>4</td>
<td>47 (PR)</td>
<td>18 (PD)</td>
<td>14 (PD)</td>
</tr>
<tr>
<td>5</td>
<td>15 (NK)</td>
<td>None</td>
<td>3 (PR)</td>
</tr>
<tr>
<td>6</td>
<td>68 (PR)</td>
<td>13 (NC)</td>
<td>18 (NC)</td>
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<tr>
<td>7</td>
<td>39 (PR)</td>
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</tr>
<tr>
<td>8</td>
<td>45 (CR)</td>
<td>10 (NC)</td>
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<td>16 (PR)</td>
<td>6 (PD)</td>
<td>34 (PR)</td>
</tr>
<tr>
<td>20</td>
<td>20 (PR)</td>
<td>None</td>
<td>81 (CR)</td>
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</table>

*CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; NK, not known (see text).

Chemotherapy was methotrexate, mitozantrone, and mitomycin C combination.

4 = OH = androstenedione.

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**Table 2** Pharmacokinetic parameters of idoxifene following administration of a single oral dose to breast cancer patients (n = 5; mean; bars, SEM).

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Cmax (ng/ml)</th>
<th>Terminal half-life (h)</th>
<th>AUC0–192h (ng • h/ml)</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>12.8 ± 1.2</td>
<td>167.8 ± 43.0</td>
<td>758.7 ± 109.8</td>
</tr>
<tr>
<td>20</td>
<td>28.9 ± 7.0</td>
<td>187.9 ± 81.9</td>
<td>1393.1 ± 280.1</td>
</tr>
<tr>
<td>40</td>
<td>60.1 ± 5.6</td>
<td>192.2 ± 34.0</td>
<td>3281.7 ± 348.7</td>
</tr>
<tr>
<td>60</td>
<td>90.7 ± 11.6</td>
<td>195.3 ± 41.0</td>
<td>5088.2 ± 607.1</td>
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</table>

Fig. 1. Plasma disposition of idoxifene after administration of single oral doses (•, 10 mg; ○, 20 mg; ▲, 40 mg; ◻, 60 mg) to breast cancer patients (n = 5; mean; bars, SEM).

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likely to confound the comparison of the effect of idoxifene. Comparisons were made only between the pretreatment value and the mean value for days 11 and 14. All values were log transformed before comparison. Significant falls were observed for LH and FSH, but no significant change was noted for E₂ and SHBG (P values: LH, 0.01; FSH, 0.03; E₂, 0.84; and SHBG, 0.20; Wilcoxon matched pairs; Table 3). To determine whether there was any evidence for a relationship between the dose of the drug and the fall in LH/FSH, two further comparisons were undertaken: (a) each dose was compared with the other, i.e., 10 mg versus 20 mg versus 40 mg versus 60 mg; and (b) given the very small size of the groups, the 10- and 20-mg groups were combined and compared with the combined 40- and 60-mg group. The Kruskal-Wallis test was applied, and in no case was there a statistically significant difference.

Results of Idoxifene Treatment

Side Effects. Overall, 14 patients complained of side effects using the questionnaire, but these were not dose related. At the 10-mg dose, three patients complained of mild nausea (lasting 20 to 30 min after idoxifene administration) and anorexia. Two of these patients vomited on two occasions, but nausea and vomiting was only seen in one other patient in the study, who was treated with 20 mg idoxifene, and this was transient. Four patients complained of tiredness, two at each of the 20- and 40-mg doses. One patient who complained of lethargy and weakness stopped treatment before the end of the 2-week treatment period. Five patients stopped treatment at the end of the 2-week treatment period due to progressive disease. The remaining 14 patients continued therapy for periods of time up to greater than 1 year (384 days).

Antitumor Effects. Of the 14 patients who remained on treatment, 4 showed stabilization of disease for 14, 8, 8, and 1.5 months, and 2 patients showed a partial response (Table 4). In one of these cases, a recurrent left axillary node showed significant reduction in size (from 40 x 40 mm to 20 x 20 mm over 4 months).
and in another patient, a supraclavicular node became impalpable after 3 months treatment and continued to be impalpable for a further 6 months. Her respiratory symptoms due to nonassessable pulmonary lymphangitis also improved very significantly. This patient, however, had not received tamoxifen previously. One patient, who experienced 12 months stable disease on idoxifene therapy, experienced a “flare” phenomenon on tamoxifen previously. No flare was observed on idoxifene.

**DISCUSSION**

Idoxifene appears to be well tolerated at the doses given to patients in the first 2 weeks of this study and caused no long-term side effects at the 20-mg dose in the patients who continued on treatment. The mild side effects that were observed were similar to tamoxifen, both in type and intensity. The prime purpose of this study was to define the toxicity of idoxifene, and very little can be concluded about its efficacy as an antimtumor agent at this time. However, disease stabilization and significant symptomatic relief was obtained using idoxifene in several patients. We cannot conclude that it is effective in patients who have become resistant to tamoxifen until a more formal Phase II study is carried out.

Qualitatively, the pharmacokinetics of idoxifene are similar to tamoxifen, reflecting the structural and physicochemical similarities of the two compounds. However, quantitatively, there are important differences in that the terminal half-life of idoxifene appears to be approximately three times longer than that reported for tamoxifen (24—26). While calculation of the clearance and volume of distribution of idoxifene were based on the assumption that the bioavailability of the drug is equal to one, comparable published data for tamoxifen has also been calculated in this way. Such data indicate idoxifene to have a lower clearance rate than tamoxifen (90 versus 189 ml/min) (27) and approximately the same volume of distribution (albeit in only three patients; Ref. 24). Previously, idoxifene has been shown to possess a longer terminal half-life than tamoxifen in the rat, which appeared to be primarily due to an increase in its volume of distribution, although it was also shown that isolated rat hepatocytes metabolized idoxifene approximately 2.5-fold more slowly than tamoxifen (17).

One of the consequences of the long terminal half-life of idoxifene is the 6—12 week treatment duration required to reach steady-state concentrations; this compares with approximately 2—6 weeks for tamoxifen (28—30). This has prompted us to investigate the use of a loading dose regimen to achieve steady-state concentrations more quickly, and these studies are ongoing. While similar studies with tamoxifen did not demonstrate any clear advantage over normal therapeutic regimen (26, 28), the longer time required to reach steady-state concentrations of idoxifene may affect the clinical outcome. The concentration of idoxifene at steady state varied widely (coefficient of variation, 33%), with a mean value of approximately 175 ng/ml for an oral dose of 20 mg daily. Literature values for the concentrations of tamoxifen at steady state, normalized to a 20-mg dose once daily, vary from 75.3—260.0 ng/ml (24, 28, 31—34). These values indicate that idoxifene attains approximately 50% higher steady-state concentrations than tamoxifen for the same dose. Considering the longer terminal half-life of idoxifene and its reduced clearance compared to tamoxifen, at least a doubling of steady-state concentrations would be predicted; however, the small number of patients studied at steady state in the present study and the large variation between them may account for this discrepancy.

The major metabolite of idoxifene observed in the rat both in vivo and in vitro was the 4’OH compound (17). Indeed, the plasma concentration of this metabolite exceeded that of the parent drug at most time points. Interestingly, this metabolite was not detected (<5.0 ng/ml) in any patient, indicating a large species difference in either its formation or its further metabolism, or both. This bears some analogy to the 4-hydroxylation of tamoxifen, which appears to be a much more important route of metabolism in rodents (particularly the mouse) than in humans (35).

Tamoxifen and other antiestrogenic triphenylethylen derivatives cause a fall in LH and FSH and an increase in SHBG levels in postmenopausal patients, which is ascribed to their partial agonist activity. Given that idoxifene has a much reduced agonist activity in animal model systems (9) and that this is potentially an important pharmacological characteristic which may have sequelae on both clinical efficacy and tolerability, it was an attractive proposition to assess the effect of idoxifene on these parameters in this study. The data demonstrate, even in this small group of patients, that there is an agonist effect of idoxifene on gonadotrophins. With the small number of patients analyzed at each dose, it was not possible to determine whether there is dose relationship with these agonist effects within the dose range of 10—60 mg/day, and at present, we cannot identify a dose which is devoid of agonist activity. The apparent lack of change in SHBG observed with idoxifene is clearly a difference between this compound and tamoxifen. The reason for this difference is not clear but is possibly due to the hepatic SHBG response element not responding to the idoxifene-activated estrogen receptor to the same extent as a tamoxifen-activated receptor. The variability of the effect between different patients precludes a quantitative comparison of these effects with published data on tamoxifen. It will, however, be important to make more detailed comparisons in the larger studies to be conducted during further drug development.

**REFERENCES**

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