Cancer Chemother Pharmacol (2004) 53: 341–348
DOI 10.1007/s00280-003-0733-6

ORIGINAL ARTICLE

S. R. D. Johnston · L. A. Gumbrell · T. R. J. Evans
R. E. Coleman · I. E. Smith · C. J. Twelves
M. Soukop · D. W. Rea · H. M. Earl · A. Howell
A. Jones · P. Canney · T. J. Powles · B. P. Haynes
B. Nutley · R. Grimshaw · M. Jarman · G. W. Halbert
M. Brampton · J. Haviland · M. Dowsett
R. C. Coombes

A Cancer Research (UK) randomized phase II study of idoxifene in patients with locally advanced/metastatic breast cancer resistant to tamoxifen

Received: 23 July 2003 / Accepted: 9 October 2003 / Published online: 13 January 2004

Abstract Idoxifene is a novel selective oestrogen receptor modulator (SERM) which had greater binding affinity for the oestrogen receptor (ER) and reduced agonist activity compared with tamoxifen in preclinical studies. In a randomized phase II trial in 56 postmenopausal patients with progressive locally advanced/metastatic breast cancer we assessed whether idoxifene showed evidence of activity compared with an increased 40 mg/day dose of tamoxifen in patients who had previously demonstrated resistance to the standard 20 mg/day dose of tamoxifen. Of 47 patients eligible for response (25 idoxifene, 22 tamoxifen), two partial responses and two disease stabilizations (SD) for >6 months were seen with idoxifene (overall clinical benefit rate 16%, 95% CI 4.5–36.1%). The median duration of clinical benefit was 9.8 months. In contrast, no objective responses were seen with the increased 40 mg/day dose of tamoxifen, although two patients had SD for 7 and 14 months (clinical benefit rate 9%, 95% CI 1.1–29.2%). Idoxifene was well tolerated and the reported possible drug-related toxicities were similar in frequency to those with tamoxifen (hot flushes 13% vs 15%, mild nausea 20% vs 15%). Endocrine and lipid analysis in both groups showed a similar significant fall in serum follicle-stimulating hormone and luteinizing hormone after 4 weeks, together with a significant rise in sex hormone binding globulin levels and 11% reduction in serum cholesterol levels. In conclusion, while idoxifene was associated with only modest evidence of clinical activity in patients with tamoxifen-resistant breast cancer, its toxicity profile and effects on endocrine/lipid parameters were similar to those of tamoxifen.

Keywords Breast cancer · Tamoxifen · Idoxifene · Tamoxifen resistance

This work is presented on behalf of the Cancer Research UK Phase I/II Committee.

S. R. D. Johnston · L. A. Gumbrell · T. R. J. Evans
R. E. Coleman · I. E. Smith · C. J. Twelves · M. Soukop
D. W. Rea · H. M. Earl · A. Howell · A. Jones · P. Canney
T. J. Powles · B. P. Haynes · B. Nutley · R. Grimshaw
M. Jarman · G. W. Halbert · M. Brampton · J. Haviland
M. Dowsett · R. C. Coombes
Cancer Research UK, Lincoln's Inn Fields,
London, WC2A 3PX, UK

R. C. Coombes (✉)
Cancer Cell Biology Section, Department of Cancer Medicine,
Division of Medicine, Faculty of Medicine ,
Imperial College, Hammersmith Hospital,
6th Floor, MRC Cyclotron Building, Du Cane Road,
London, W12 0NN, UK
E-mail: c.coombes @ic.ac.uk
Tel.: +44-20-83835828
Fax: +44-20-83835830

Introduction

Tamoxifen is an effective antioestrogen for the treatment of advanced breast cancer with objective responses seen in approximately 60–70% of untreated patients positive for oestrogen receptor (ER) [1]. Tamoxifen given as adjuvant therapy after early breast cancer significantly improves both recurrence-free and overall survival [2]. However, many patients develop acquired resistance and progress despite an initial response to tamoxifen given for advanced disease, or relapse following several years of adjuvant therapy. It has been demonstrated that functional ER continues to be expressed in many of these tumours [3, 4] and that response to further endocrine therapy such as oral aromatase inhibitors or pure antioestrogens often occurs in such patients [5, 6]. Several mechanisms for acquired resistance specific to tamoxifen have been proposed, including tumour

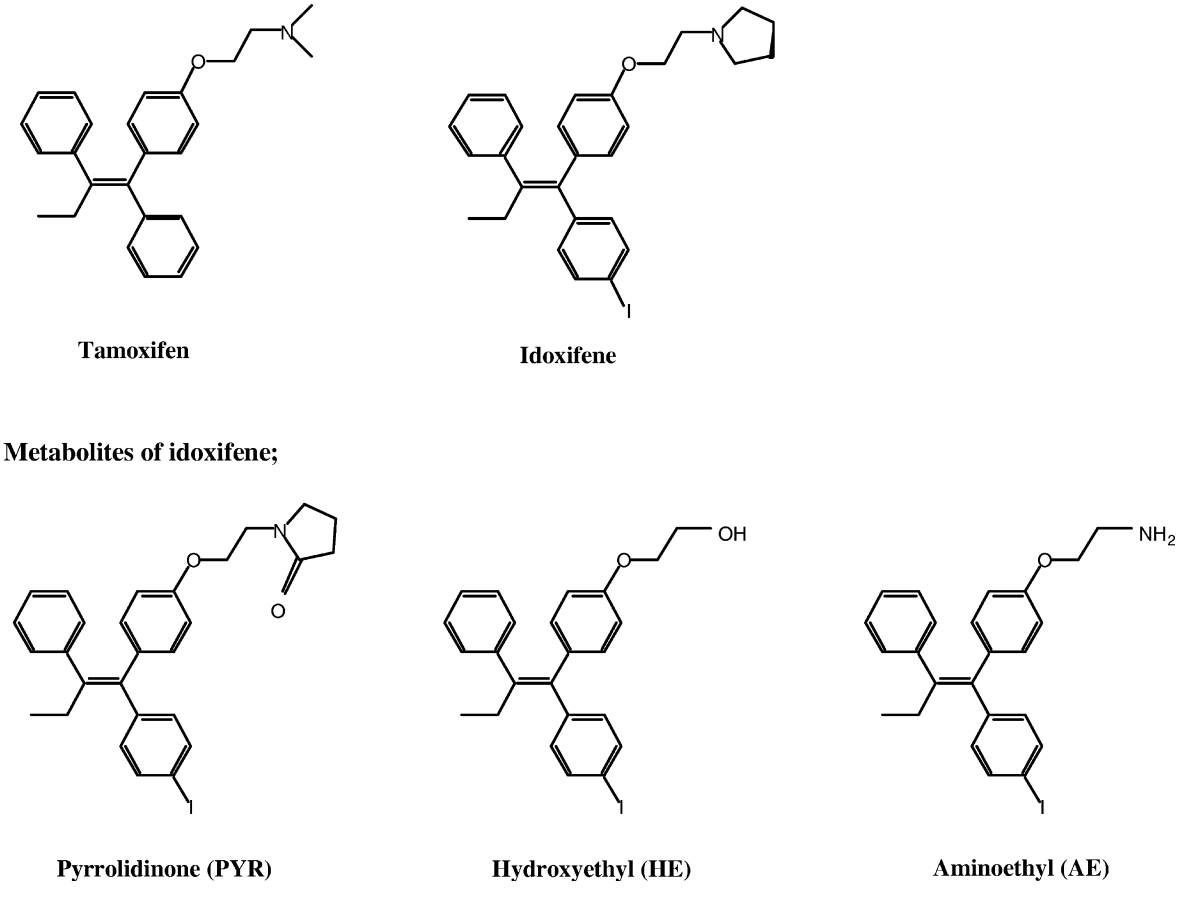
stimulation by the agonist properties of tamoxifen and/or its metabolites [7, 8].

Idoxifene, a novel selective ER modulator (SERM) which is structurally related to tamoxifen (Fig. 1), is a metabolically more stable antioestrogen with increased affinity for the ER [9, 10]. Idoxifene has been shown to inhibit hormone-dependent breast cancer cells in vitro, and is more effective than tamoxifen at inhibiting rat mammary tumour growth in vivo [10]. Its reduced agonist activity compared with tamoxifen has been demonstrated in the immature rat uterotrophic assay [10], and these findings suggest that the drug could be an effective antioestrogen in circumstances when tamoxifen's agonist activity may be predominant. In the absence of oestradiol, idoxifene inhibits the growth of MCF-7 breast cancer xenografts significantly more than tamoxifen, which in turn is associated with a reduced frequency of tumours which develop acquired antioestrogen resistance [8].

In a phase I study idoxifene has been shown to have linear pharmacokinetics with a terminal half-life of approximately 3 weeks, with steady-state concentrations of idoxifene 50% higher than those of tamoxifen given at the same dose [11]. Of 14 patients who had previously received tamoxifen, two patients had a partial response (PR) with idoxifene and three patients had disease stabilization (stable disease, SD) for > 6 months. It is well recognized with endocrine therapy that breast cancer patients who achieve SD for 6 months or more have a similar prognosis to those with an objective PR [12].

For patients who relapse on tamoxifen 20 mg/day, there are some previous reports that they may achieve SD for at least 6 months if treated with higher doses of tamoxifen [13, 14, 15]. It was decided in this double-blind phase II study to randomize patients relapsing following tamoxifen 20 mg/day who were suitable for further endocrine therapy either to idoxifene 40 mg/day or to an increased 40 mg/day dose of tamoxifen. The aims of the study were to determine whether idoxifene was non-cross-resistant with tamoxifen which had been given at standard doses, and to establish idoxifene's side effect profile in this setting. In addition to clinical efficacy and safety data, changes in endocrine and lipid parameters were measured in order to compare the oestrogen-like agonist activity of idoxifene with that of tamoxifen on these non-breast-related biological endpoints.

Fig. 1 Chemical structures of tamoxifen and idoxifene, together with the main metabolites of idoxifene



Patients and methods

Patient eligibility and trial design

A total of 56 patients from eight centres with locally advanced/metastatic breast cancer who had previously become resistant to tamoxifen 20 mg/day were registered and randomized into the

study. All patients were postmenopausal, had progressive disease and were required to have an ER status which was positive or unknown. If there was less than 1 year since the last menstrual period, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) had to be >40 IU/l. Patients were eligible provided they had either received tamoxifen 20 mg/day previously for advanced disease having demonstrated an objective response or disease stabilization for >6 months prior to progression on tamoxifen, or had received adjuvant tamoxifen 20 mg/day for at least 2 years and subsequently relapsed while still on tamoxifen. In addition, patients were eligible if they had received tamoxifen for advanced disease and progressed without any response but were ER-positive. Other subsequent endocrine therapy for advanced disease was allowed provided patients had responded or stabilized for >6 months to such therapy. Patients were required to have measurable disease with an ECOG performance status of <2. The patient characteristics in the two treatment groups are shown in Table 1.

The design was a double-blind double-dummy randomized phase II study. Idoxifene was supplied as gelatine capsules prepared by the Cancer Research Campaign Formulation Unit, University of Strathclyde, UK (Dr. Gavin Halbert). Patients were randomized to receive either idoxifene capsules or tamoxifen tablets, together with a placebo drug (given as tablets for those receiving idoxifene capsules, or as capsules for those receiving tamoxifen tablets). In view of the long half-life of idoxifene (21 days) a loading dose schedule of 60 mg/day for 14 days was used. Therefore, patients who were randomized to idoxifene received three idoxifene 20 mg capsules plus two placebo tablets for 2 weeks, followed by two idoxifene capsules plus two placebo tablets. Those randomized to tamoxifen received three placebo capsules for 2 weeks plus two tamoxifen 20 mg tablets, followed for the remainder of the study by two placebo capsules and two tamoxifen tablets.

Clinical assessment

The primary objective of the study was to determine the response rate, time to progression and survival in the two arms of the study. Patients were required to have measurable disease defined by at least one bidimensionally measurable lesion, and response was assessed according to standard UICC criteria [16]. Patients who showed SD for at least 6 months were included in the assessment of clinical benefit. All tumour responses were subject to independent peer review prior to the study code being broken. Time to progression and overall survival were assessed from the date of randomization until documentation of disease progression or death, respectively.

The secondary aim was to determine the side effects of treatment in both groups. Toxicity was recorded at each clinic visit using the NCIC-CTG Expanded Common Toxicity Criteria. Samples for routine haematology and biochemistry were taken every 4 weeks.

Pharmacokinetics

Plasma samples were taken at 0, 2, 4, 8 and 12 weeks from a total of 48 patients (25 idoxifene, 23 tamoxifen). Samples of plasma (0.5 ml) were mixed with 0.5 ml acetonitrile and the precipitated protein was removed by centrifugation (13,000 rpm for 2 min). The supernatant was extracted with 6 ml hexane/butanol (98:2) and the extracts evaporated to dryness at 40°C under nitrogen. The dried extracts were reconstituted in 200 µl eluent and 10 µl was subjected to high-pressure liquid chromatography (HPLC) according to previously published methodology [9]. The assay was fully validated for tamoxifen, idoxifene and their major metabolites in the concentration range 10–1000 ng/ml.

Endocrine and lipid analyses

Oestradiol and sex hormone binding globulin (SHBG) were measured according to previously reported methodologies [17, 18]. LH and FSH were measured using an Axsym immunoassay system (Abbott Laboratories, Abbott Park Ill.), and cholesterol using a CX9 system (Beckman, Fullerton, Calif.). Insulin-like growth factor-1 (IGF-1) was measured using an immunoradiometric assay (DSL-2800) from Diagnostic System Laboratories (Webster, Tx.). Interassay CV ranged from 4.2% to 7.4%, with a sensitivity of 0.25 nmol/l.

Statistical considerations

A sample size of 164 patients was proposed in the original study protocol based on an estimated clinical benefit rate, i.e. complete response (CR), PR and SD for >6 months, of 35% in the 40 mg/day tamoxifen arm as reported in the two previous studies of

Table 1 Patient characteristics

		Idoxifene	Tamoxifen
No. of patients		30	26
Age (years)	Median	61.5	69.5
	Range	46–82	38–85
Median performance status		0	0
Form of tamoxifen treatment			
Adjuvant	No. of patients	17	15
	Duration (months)		
	Median	48	47.5
	Range	26–142	22–116
Metastatic	No. of patients	13	11
	Prior response		
	CR/PR	9	7
	NC	3	2
	PD (but ER^+)	1	1
Prior other endocrine therapy for metastatic disease	No. of patients	8	6
	Time since tamoxifen (months)		
	Median	23	15
	Range	7–52	4–43
ER status	Positive	14	10
	Unknown	16	16

increased tamoxifen dose [13, 14]. The sample size was calculated with an initial aim of detecting a 25% difference in efficacy (two-sided at the 5% significance level with 90% power). An independent Data Monitoring Committee (DMC) was established at the outset of the trial to monitor the clinical data. Following an initial review of the first 36 patients in July 1997 and due to slow recruitment, the DMC recommended that the study size be modified to 25 patients in each arm in order to better define the response rate (i.e. according to two parallel standard Gehan phase II studies). As a consequence of the reduced sample size, the clinical data are presented from this double-blind randomized trial as a phase II study of idoxifene in patients resistant to tamoxifen 20 mg/day, with those randomized to tamoxifen 40 mg/day as the reference arm without any statistical comparisons between the two treatment groups.

Clinical efficacy is reported as the clinical benefit rate (CR, PR and SD >6 months), and was estimated with associated 95% confidence intervals. Toxicities are expressed as categorical data. The significance of any change in endocrine or lipid parameters from baseline to 4 or 12 weeks, respectively, was analysed by Wilcoxon's signed-ranks test. The extent of any difference between baseline and treatment in these parameters was then compared between the tamoxifen and idoxifene groups by the Mann-Whitney test.

Results

Clinical efficacy

There were 47 patients with confirmed resistance to prior tamoxifen 20 mg/day eligible for assessment of tumour response (25 idoxifene, 22 tamoxifen). The reasons for ineligibility included no drug received following randomization (two idoxifene, zero tamoxifen), no measurable/evaluable disease (one idoxifene, zero tamoxifen), no response to other prior endocrine therapies as defined in the protocol (one idoxifene, three tamoxifen), and no confirmed resistance to tamoxifen (one idoxifene, one tamoxifen).

There were two PRs and two SDs for >6 months in those treated with idoxifene, giving an overall clinical benefit rate of 16% (95% CI 4.5–36.1%). The duration of the PRs was 30 months in a patient with recurrent breast and chest wall nodules, and 5 months in another patient with skin nodules (Table 2). SD was seen in one patient with a breast recurrence and bone metastases for 7 months, while another patient had measurable lung metastases which were stable for 13 months. Of these four patients, two had true acquired resistance having demonstrated either a PR or a CR to tamoxifen previously for between 2 and 7 years, while the other two had received between 30 and 60 months of adjuvant tamoxifen (Table 2). Overall, for all 30 patients treated with idoxifene, the time to disease progression was 2.6 months (95% CI 0.2–5.0 months), with a median survival of 18.6 months (95% CI 12.3–24.9 months).

For those treated with tamoxifen 40 mg/day following progression on tamoxifen 20 mg/day, no objective responses (CR/PR) were seen. Two patients had SD for >6 months (clinical benefit rate 9%, 95% CI 1.1–29.2%). Both patients had ER-positive disease, and stabilization was seen in either mediastinal nodes/pleural disease and locally recurrent disease for 7 and 14 months, respectively (Table 2). Overall, for the 26 patients treated with tamoxifen 40 mg/day, the median time to disease progression was 2.8 months (95% CI 1.9–3.5 months), with a median survival of 21.3 months (95% CI 16.1–26.6 months).

Toxicity

Both drugs were well tolerated. The most frequently observed possible drug-related side effects are shown in Table 3. Mild (grade 1/2) nausea was reported in 20% and 15% of patients treated with idoxifene and tamoxifen, respectively. Possible endocrine-associated side effects included hot flushes, but these were similar in incidence between the two groups (13% and 15%, respectively). One patient in each group had possible tumour flare reactions (increase in bone/soft tissue pain) following initiation of therapy. There was one episode of urticaria in the idoxifene-treated group, although the patient had a preexisiting condition which was exacerbated during therapy.

Table 2 Sites of response, response duration and prior history of endocrine therapy in patients with objective response or disease stabilization

	Patient no.	Age (years)	ER status	Response/reason for prior tamoxifen	Sites of disease at study entry	Response	Response duration (months)
Idoxifene	32	78	Positive	Partial response (7 years) for locally advanced breast cancer	Breast, chest wall nodules	PR	30
	41	49	Unknown	Adjuvant (2.5 years)	Skin nodules	PR	5
	46	75	Unknown	Complete response (2 years) for locally advanced breast cancer	Local recurrence in breast, bone metastases	SD	7
	55	59	Unknown	Adjuvant (5 years)	Lung, bone	SD	13
Tamoxifen	6	70	Positive	Progressive disease (5 months) for locally advanced breast cancer	Breast	SD	14
	28	38	Positive	Adjuvant (2 years)	Mediastinal nodes, pleural mass	SD	7

Table 3 Patients with possible drug-related toxicities as assessed by the NCIC-CTG expanded common toxicity criteria

Toxicity	Idoxifene ($n=30$)	Tamoxifen ($n=26$)
Hot flushes	4 (13%)	4 (15%)
Mild nausea (grade 1/2)	6 (20%)	4 (15%)
Urticaria	1 (3%)	0 (0%)
Tumour flare	1 (3%)	1 (4%)
Lethargy	0 (0%)	2 (8%)
Arthralgia	2 (7%)	0 (0%)
Dyspnoea	1 (3%)	0 (0%)
Diarrhoea	0 (0%)	1 (4%)
Itching skin (grade 1)	1 (3%)	1 (4%)
Indigestion (grade 1)	1 (3%)	1 (4%)
Depression	2 (6%)	0 (0%)
Minor per vaginal bleeding	2 (6%)	0 (0%)
Insomnia	1 (3%)	0 (0%)

Pharmacokinetics

Pharmacokinetic analyses were performed in a total of 48 patients (25 idoxifene, 23 tamoxifen). In prestudy plasma samples, tamoxifen and its metabolites could be detected in approximately half of the patients, with a mean tamoxifen concentration of 93 ± 24 ng/ml.

Mean idoxifene plasma concentrations after the loading dose period (60 mg/day for 2 weeks) were 278 ± 27 ng/ml which then reached 393 ± 41 ng/ml by 12 weeks. Comparison of paired 8- and 12-week samples in nine idoxifene-treated patients showed that there was only a $13 \pm 6\%$ increase over this period, suggesting that near steady-state had been reached. Three metabolites of idoxifene were identified by comparison with standards synthesized in the Department of Chemistry at the Institute of Cancer Research: the deaminated hydroxyethyl side-chain (HE), the ring-oxidized pyrrolidinone (PYR), and the aminoethyl side-chain compounds (AE) [19]. By 12 weeks the levels of HE (306 ± 25 ng/ml) and PYR (123 ± 12 ng/ml) were probably sufficient to contribute to idoxifene's biological effect as both have relative binding affinities (RBA) for ER lower than that of idoxifene but similar to that of tamoxifen: RBA 2.6 HE, 4.2 PYR, 12.0 idoxifene, 4.5 tamoxifen [19]. While the levels of the PYR and AE metabolites appeared to have reached steady-state by 12 weeks, levels of the HE metabolite appeared to still be rising (Fig. 2).

Mean tamoxifen plasma concentrations at 12 weeks were 270 ± 46 ng/ml which appeared to have reached steady-state (Fig. 3). The major metabolites of tamoxifen were N-desmethyltamoxifen (DMT) and di-desmethyltamoxifen (DDMT). After 12 weeks these reached mean levels of 556 ± 66 ng/ml and 97 ± 11 ng/ml, respectively. Our assay system was not able to detect significant levels of 4-hydroxytamoxifen which is known to only exist at approximately 1–2% of the plasma level of tamoxifen.

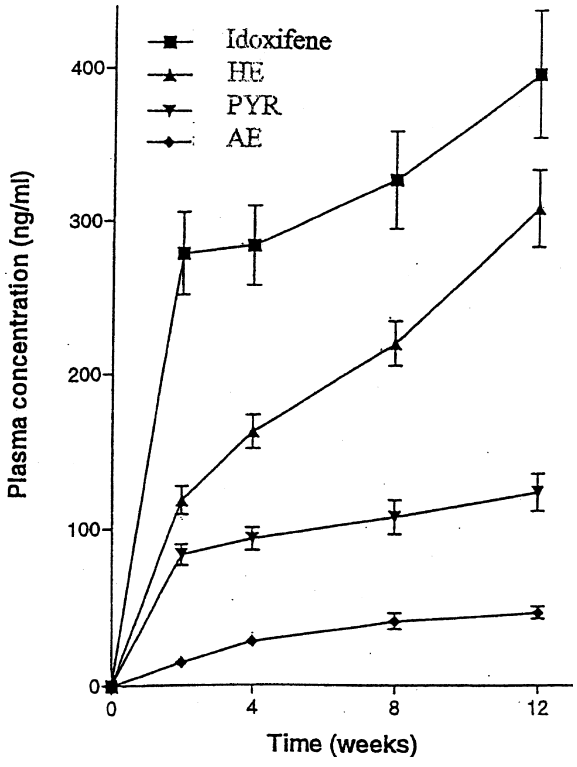


Fig. 2 Mean (±SEM) plasma concentrations of idoxifene and its three metabolites (HE, PYR, AE) during daily dosing with 60 mg orally for 14 days and 40 mg orally daily thereafter ($n=25$)

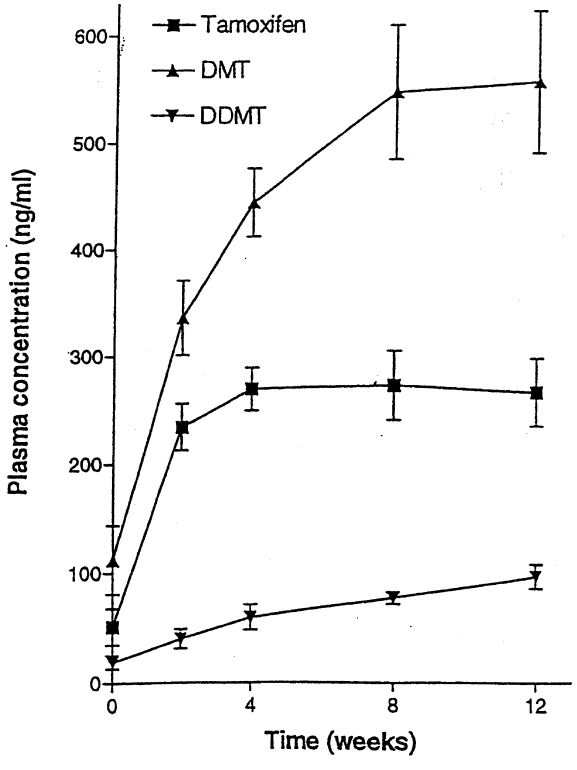


Fig. 3 Mean (±SEM) plasma concentrations of tamoxifen and its two metabolites (DMT, DDMT) during daily dosing with 40 mg orally ($n=23$)

Endocrine and lipid profile

In those patients who recently stopped tamoxifen just prior to study entry there was no significant change in levels of LH, FSH, SHBG, cholesterol, IGF1 or oestradiol (data not shown). However, baseline levels of SHBG were higher in these patients compared with those entered with >3 months since prior tamoxifen, consistent with the persistent biological effects of prior tamoxifen therapy on these parameters (baseline SHBG 82.2 ± 7.1 nmol/l in the idoxifene group and 101.1 ± 12.1 nmol/l in the tamoxifen group, which are significantly higher than the baseline values in Table 4 for those patients at least 3 months off tamoxifen). Similar differences with suppression of baseline LH and FSH values were seen in those who had just completed tamoxifen compared to those >3 months off therapy.

In patients who entered the study >3 months since the last tamoxifen dose ($n = 8$ randomized to idoxifene, $n = 9$ randomized to tamoxifen), an effect of the study drug on endocrine or lipid parameters might be expected. There was a significant fall in both FSH and LH levels following 4 weeks of either idoxifene or tamoxifen (Table 4). Likewise, SHBG levels increased following either idoxifene (median +22.5 nmol/l) or tamoxifen (median +29.5 nmol/l). After 12 weeks there was an 11% (0.5 nmol/l) reduction in total cholesterol in patients >3 months since prior tamoxifen exposure who were treated with either idoxifene or an increased dose of tamoxifen, although this failed to reach statistical significance. There were no major differences in serum oestradiol or IGF-1 levels (Table 4).

Discussion

In this double-blind randomized phase II study we showed that idoxifene, a novel nonsteroidal antioestrogen with reduced agonist activity on breast and uterine tissues in preclinical models, may have some clinical efficacy in patients who have developed resistance to previous tamoxifen. It is recognized that a proportion of tumours in such patients retain a functional ER [3, 4], and that responses to further endocrine therapy such as aromatase inhibitors or progestins occur following failure on tamoxifen [5, 20]. There is experimental evidence that acquired resistance to tamoxifen in some instances may relate to the drug's partial agonist properties [21]. Thus there is a rationale to examine whether nonsteroidal antioestrogens with reduced agonist activity demonstrate any clinical activity in patients who develop resistance to tamoxifen.

The agonist properties of tamoxifen were originally thought to relate to oestrogenic metabolites such as metabolite E and bisphenol formed by removal of the side-chain together with hydroxylation at position 4 [22]. Equally, there are reports that enhanced metabolism of tamoxifen could account for loss of efficacy with reduced intratumoral levels of tamoxifen in tumours with acquired resistance [23, 24, 25]. Idoxifene was developed as an antioestrogen with both enhanced affinity for ER due to the iodine atom at position 4 (Fig. 1) which blocks metabolism at this position [26] and reduced side-chain metabolism as a consequence of the pyrrolidino ring [9, 27]. More recent data, however, invalidate this concept and are consistent with our observations that no oestrogenic metabolites are found in our patients [28, 29, 30].

In our study in which 47 patients had confirmed resistance to tamoxifen, we observed two PRs and two SDs for >6 months. As illustrated in Table 2, prior responses to tamoxifen or a prolonged disease-free interval during adjuvant therapy had been seen in these patients, compatible with a phenotype of acquired resistance. Overall, the number of known ER-positive patients was relatively low in this study (43%), with ER status unknown in the remainder. Although patients were selected as suitable for further endocrine therapy based on the clinical eligibility criteria outlined above, the relatively low response rate overall may partially be accounted for by a proportion of patients with ER-negative tumours in the unknown group. In two of the randomized phase III trials of aromatase inhibitors (either anastrozole or letrozole) versus megestrol acetate following tamoxifen failure, reported ER-positivity rates were also only approximately 50% with the ER status in a significant proportion of randomized patients being

Table 4 LH, FSH, SHBG, cholesterol, IGF-1 and oestradiol before and after 4 weeks (12 weeks for cholesterol) treatment with either idoxifene (40 mg/day) or tamoxifen (40 mg/day) in patients at least 3 months since prior tamoxifen dose at study entry ($n = 8$ idoxifene, $n = 9$ tamoxifen). Values are means ± SEM (Δ median change in each parameter following treatment, with significance assessed by Wilcoxon's signed ranks test, *NS* not significant)

	Idoxifene			Tamoxifen		
	Before treatment	After treatment	Δ (significance)	Before treatment	After treatment	Δ (significance)
LH (IU/l)	35.1 ± 5.3	23.0 ± 3.7	−13.8 ($P = 0.03$)	26.4 ± 6.9	12.5 ± 3.3	−11.5 ($P = 0.04$)
FSH (IU/l)	52.5 ± 9.6	34.3 ± 6.2	−14.4 ($P = 0.009$)	32.9 ± 7.3	20.1 ± 3.9	−10.5 ($P = 0.02$)
SHBG (nmol/l)	60.1 ± 10.7	80.4 ± 14.3	+22.5 ($P = 0.05$)	79.0 ± 19.4	94.3 ± 20.2	+29.5 ($P = 0.09$)
IGF-1 (nmol/l)	17.1 ± 3.5	13.0 ± 3.0	−3.0 (NS)	15.4 ± 2.3	12.4 ± 2.3	−6.0 ($P = 0.04$)
Oestradiol (pmol/l)	40.9 ± 8.2	47.8 ± 12.3	−4.0 (NS)	34.0 ± 9.5	19.3 ± 5.5	−3.0 (NS)
Cholesterol (nmol/l)	4.8 ± 0.1	4.3 ± 0.1	−0.5 (NS)	4.7 ± 0.6	4.2 ± 0.5	−0.5 (NS)

unknown [5, 19]. In these trials the objective response rates to further second-line therapy ranged from 8% to 23% with SD in a further 15–25%. This gives a clinical benefit rate which may range from 23% to 48%, which although higher than that observed in our relatively small trial, does cross the 95% CI range for the clinical benefit seen with idoxifene. These second-line endocrine response data are also for the pure steroidal antioestrogen ICI 182,780 (Faslodex) in a non-randomized phase II study in 19 patients with acquired resistance to tamoxifen [31].

An increased dose (40 mg/day) of tamoxifen was not associated with any objective responses in patients resistant to tamoxifen 20 mg/day. There have been three previous phase II studies in a total of 81 patients with metastatic breast cancer whose disease was resistant to tamoxifen 20 mg/day, and who were subsequently treated with 40–90 mg/day tamoxifen at progression [13, 14, 15]. Overall PRs were seen in only three patients (4%), while a further 36 patients (44%) had SD. However, in these non-randomized studies "no change" was not defined as a minimum of 6 months. We are not aware of any previous double-blind randomized studies of increased tamoxifen dose following failure of 20 mg/day. Our results suggest that objective remissions do not occur or are infrequent, although a small proportion of patients may have disease stabilization for >6 months.

The major metabolites of idoxifene which we detected in this study include the hydroxyethyl (HE), pyrrolidone (PYR), and aminoethyl (AE) derivatives which all retain an intact iodine at position 4 and represent products of side-chain metabolism (Fig. 2). These metabolites have RBA values lower than that of idoxifene but equivalent to that of tamoxifen [19, 32]. In this study plasma levels of the HE, PYR and AE metabolites were 88%, 31% and 14% of idoxifene, respectively, such that they probably contribute to idoxifene's overall antioestrogenic activity in vivo. The major route of tamoxifen metabolism in humans is deamination to give N-desmethyltamoxifen (DMT) and di-desmethyltamoxifen (DDMT) which at steady-state exist at approximately 150% and 30% of parent compound levels, respectively [33, 34]. The relative levels of metabolites in our study were in keeping with these previous reports, while the steady-state levels for tamoxifen were approximately double those reported for the standard 20 mg/day dose [35]. While the DMT and DDMT metabolites have lower RBA values for ER than tamoxifen, their plasma levels are sufficiently high that they probably also contribute to the antioestrogenic activity of the drug as a whole.

Tamoxifen is known to elevate SHBG levels and suppress LH and FSH in postmenopausal women due to its agonist effect on the liver and pituitary gland, respectively [36, 37, 38]. In this randomized phase II study we established that idoxifene had similar effects to tamoxifen on levels of LH/FSH, SHBG and cholesterol (Table 4). It was only possible to detect significant changes in these parameters in those 17 patients in whom prior tamoxifen therapy had ceased at least 3 months prior to study entry due to other intervening endocrine therapy. Baseline elevation of SHBG and suppression of LH/FSH was observed in those patients entering the study <5 weeks since prior tamoxifen, due to the persistent biological effects of prior tamoxifen therapy on these parameters, and as such these values did not change on study. Other clinical data exist for idoxifene in postmenopausal women which show tamoxifen-like beneficial effects on markers of bone turnover [39] together with a reduction in cholesterol [40], consistent with the profile of the drug as a SERM.

During the preparation of this report, a phase III study was published [41] in which 219 patients with untreated metastatic breast cancer were randomized to receive idoxifene or tamoxifen. No significant differences were observed in overall response rates (34.3% for idoxifene, 38.7% for tamoxifen) or time to progression.

In conclusion, this double-blind randomized phase II trial demonstrated that idoxifene was associated with evidence of clinical activity in a proportion of patients with tamoxifen-resistant advanced breast cancer. However, the clinical benefit rate seen with idoxifene was modest in comparison that observed with current third-generation aromatase inhibitors following tamoxifen failure. In contrast, there was no evidence of any objective responses to an increased dose of 40 mg/day tamoxifen in those resistant to 20 mg/day.

Acknowledgements This study was conducted by the Cancer Research Campaign. We acknowledge the support of Judith Bliss from the Institute of Cancer Research in the analysis of data and statistical support. The pharmacokinetic, endocrine and lipid analyses were supported by a separate programme grant from the Cancer Research Campaign to the CRC Centre for Cancer Therapeutics and the Department of Academic Biochemistry at the Institute of Cancer Research and Royal Marsden Hospital. Dr. Ray McCague and Dr. Ian Hardcastle from the CRC Centre for Cancer Therapeutics isolated and synthesized the metabolites of idoxifene. Idoxifene was subsequently licensed to SmithKline Beecham Pharmaceuticals through the British Technology Group.

References

1. McGuire WL (1978) Hormone receptors; their role in predicting prognosis and response to endocrine therapy. Semin Oncol 5:428
2. Early Breast Cancer Trialists Group (1998) Tamoxifen for early breast cancer; an overview of the randomised trials. Lancet 351:1451
3. Encarnacion CA, Ciocca DR, McGuire WL, Clark GM, Fuqua SA, Osborne CK (1993) Measurement of steroid hormone receptors in breast cancer patients on tamoxifen. Breast Cancer Res Treat 26:237
4. Johnston SRD, Saccani-Jotti G, Smith IE, Salter J, Newby J, Coppen M, Ebbs SR, Dowsett M (1995) Changes in oestrogen receptor, progesterone receptor and pS2 expression in tamoxifen-resistant human breast cancer. Cancer Res 55:3331
5. Buzdar A, Jonat W, Howell A, Jones SE, Blomqvist C, Vogel CL, Eiermann W, Wolter JM, Azab M, Webster A, Plourde PV (1996) 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 14:2000

6. Howell A, De Friend D, Robertson J, Blamey R, Walton P (1995) Response to the pure antioestrogen ICI 182,780 in tamoxifen resistant breast cancer. Lancet 345:29
7. Howell A, Dodwell DJ, Laidlaw I (1990) Tamoxifen as an agonist for metastatic breast cancer. In: Goldhirsch A (ed) Endocrine therapy of breast cancer. Springer Verlag, New York, p 49
8. Johnston SRD, Riddler S, Haynes BP, A'Hern R, Smith IE, Jarman M, Dowsett M (1997) The novel antioestrogen idoxifene inhibits the growth of human MCF-7 breast cancer xenografts and reduces the frequency of acquired antioestrogen resistance. Br J Cancer 75:804
9. Johnston SR, Haynes BP, Sacks NP, McKinna JA, Griggs LJ, Jarman M, Baum M, Smith IE, Dowsett M (1993) Effect of oestrogen receptor status and time on the intra-tumoural accumulation of tamoxifen and N-desmethyltamoxifen following short-term therapy in human primary breast cancer. Breast Cancer Res Treat 28:241
10. Chander SK, McCague R, Luqmani Y, Newton C, Dowsett M, Jarman M, Coombes RC (1991) Pyrrolidino-4-iodotamoxifen and 4-iodotamoxifen, new analogues of the antioestrogen tamoxifen for the treatment of breast cancer. Cancer Res 51:5851
11. Coombes RC, Haynes BP, Dowsett M, Quigley M, English J, Judson IR, Griggs LJ, Potter GA, McCague R, Jarman M (1995) Idoxifene: report of a phase I study in patients with metastatic breast cancer. Cancer Res 55:1070
12. Howell A, Mackintosh J, Jones M, Redford J, Wagstaff J, Sellwood RA (1998) 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 24:1567
13. Goldhirsch A, Joss RA, Leuenberger U, Cavalli R, Ryssel HJ, Brunner KW (1982) An evaluation of tamoxifen dose escalation in advanced breast cancer. Am J Clin Oncol 5:501
14. Stewart JF, Minton MJ, Rubens RD (1982) Trial of tamoxifen at a dose of 40 mg daily after disease progression during tamoxifen therapy at a dose of 20 mg daily. Cancer Treat Rep 66:1445
15. Watkins SM (1988) The value of high dose tamoxifen in postmenopausal breast cancer patients progressing on standard doses: a pilot study. Br J Cancer 57:320
16. Hayward JL, Carbone PP, Heuson J-C, Kumaoka S, Segaloff A, Rubens RD (1977) Assessment of response to therapy in advanced breast cancer. Eur J Cancer 13:89
17. Dowsett M, Goss PE, Powles TJ, Hutchinson G, Brodie AM, Jeffcoate SL, Coombes RC (1987) Use of aromatase inhibitor 4-hydroxyandrostenedione in post-menopausal breast cancer; optimisation of therapeutic dose and route. Cancer Res 47:1957
18. Johnston SRD, Smith IE, Doody D, Jacobs S, Robershaw H, Dowsett M (1994) The clinical and endocrine effects of the oral aromatase inhibitor vorozole in postmenopausal patients with advanced breast cancer. Cancer Res 54:5875
19. Haynes BP, Grimshaw RM, Griggs LJ (1998) Pharmacokinetics of idoxifene and tamoxifen in a randomised phase II trial in breast cancer patients who have relapsed on tamoxifen. Ann Oncol 9 [Suppl 2]:177
20. Dombernowsky P, Smith IE, Falkson G, Leonard R, Panasci L, Bellmunt J, Bezwoda W, Gardin G, Gudgeon A, Morgan M, Fornasiero A, Hoffmann W, Michel J, Hatscheck T, Tjabbes T, Chaudri HA, Hornberger U, Trunet PF (1998) Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomised trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol 16:453
21. Gottardis M, Jordan VC (1998) Development of tamoxifen-stimulated growth of MCF-7 tumors in athymic mice after long-term antioestrogen administration. Cancer Res 48:5183
22. Wiebe VJ, Osborne CK, McGuire WL, DeGregorio MW (1992) Identification of oestrogenic tamoxifen metabolite(s) in tamoxifen-resistant human breast tumors. J Clin Oncol 10:990
23. Osborne CK, Coronado E, Allred DC, Wiebe V, DeGregorio M (1991) Acquired tamoxifen resistance: correlation with reduced breast tumor levels of tamoxifen and isomerisation of trans-4-hydroxytamoxifen. J Natl Cancer Inst 83:1477
24. Osborne CK, Wiebe VJ, McGuire WL, Ciocca DR, DeGregorio MW (1992) Tamoxifen and the isomers of 4-hydroxytamoxifen in tamoxifen-resistant tumors from breast cancer patients. J Clin Oncol 10:304
25. Johnston SRD, Haynes BP, Smith IE, Jarman M, Sacks NP, Ebbs SE, Dowsett M (1993) Acquired tamoxifen resistance in human breast cancer and reduced intra-tumoural drug concentration. Lancet 342:1521
26. McCague R, Parr IB, Haynes BP (1990) Metabolism of the 4-iodo derivative of tamoxifen by isolated rat hepatocytes. Biochem Pharmacol 40:2277
27. Haynes BP, Parr IB, Griggs LJ (1991) Metabolism and pharmacokinetics of pyrrolidino-4-iodotamoxifen in the rat. Breast Cancer Res Treat 19:174
28. Wolf DM, Langan-Fahey SM, Parker CJ, McCague R, Jordan VC (1993) Investigation of the mechanism of tamoxifen-stimulated breast tumour growth with nonisomerizable analogues of tamoxifen and metabolites. J Natl Cancer Inst 85:806
29. Osborne CK, Jarman M, McCague R, Coronado EB, Hilsenbeck SG, Wakeling AE (1994) The importance of tamoxifen metabolism in tamoxifen-stimulated breast tumour growth. Cancer Chemother Pharmacol 34:89
30. Lee ES, Schafer JM, Yao K, England G, O'Regan RM, De Los Reyes A, Jordan VC (2000) Cross-resistance of triphenylethylene-type antiestrogens but not in ICI 182,780 in tamoxifen-stimulated breast tumours grown in athymic mice. Clin Cancer Res 6:4893
31. Howell A, Robertson JF, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, Vergote I, Erikstein B, Webster A, Morris C (2002) Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 20:3396
32. Hardcastle IR, Rowlands MG, Houghton J (1995) 4′-Substituted analogues of idoxifene; antioestrogens and calmodulin antagonists. Biorganic Med Chem Lett 5:805
33. Langhan-Fahey SM, Tormey DC, Jordan VC (1990) Tamoxifen metabolites in patients on long-term adjuvant therapy for breast cancer. Eur J Cancer 26:883
34. Patterson JS, Settatree RS, Adam HK, Kemp JV (1980) Serum concentrations of tamoxifen and major metabolites during long-term Nolvadex therapy, correlated with clinical response. In: Mouridsen HT, Palshof T (eds) Breast cancer—experimental and clinical aspects. Pergamon Press, Oxford, p 89
35. Bratherton DG, Brown CH, Buchanan RB, Hall V, Kingsley Pillers EM, Wheeler TK, Williams CJ (1984) A comparison of two doses of tamoxifen (Nolvadex) in post-menopausal women with advanced breast cancer. Br J Cancer 50:199
36. Jordan VC, Fritz NF, Tormey DC (1987) Long-term adjuvant therapy with tamoxifen: effects on sex hormone binding globulin and antithrombin III. Cancer Res 47:4517
37. McFadyen IJ, Raab G, Forrest AP, Langlands AO, Stewart HJ, Roberts MM, Hamilton T, Golder MP, Groom GV, Griffiths K (1979) The effect of tamoxifen and stilboestrol on plasma hormone levels in post-menopausal women with advanced breast cancer. Clin Oncol 5:251
38. Love RR, Newcomb PA, Wiebe DA, Surawicz TS, Jordan VC, Carbone PP, DeMets DL (1990) Effects of tamoxifen therapy on lipid and lipoprotein levels in post-menopausal women with node-negative breast cancer. J Natl Cancer Inst 82:1327
39. Delmas P, Mulder H, Eastell R, et al (1998) Idoxifene reduces bone turnover in osteopenic postmenopausal women. Bone 23:S494
40. Mulder H, Wasnich R, Eastell R, et al (1998) The effects of idoxifene on markers of cardiovascular risk in osteopenic postmenopausal women. Eur Heart J 19:237
41. Arpino G, Nair Krishnan M, Doval Dinesh C, Bardou VJ, Clark GM, Elledge RM (2003) Idoxifene versus tamoxifen: a randomized comparison in postmenopausal patients with metastatic breast cancer. Ann Clin Oncol 14:233