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Original Paper

Onapristone, a Progesterone Receptor Antagonist, as First-line Therapy in Primary Breast Cancer

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The progesterone receptor antagonist, Onapristone, is an effective endocrine agent in experimental breast cancer models. This study aimed to investigate this agent as first-line endocrine therapy in patients with breast cancer. However, owing to the recognition in this and other clinical studies that some patients on Onapristone developed liver function test abnormalities, the development of this drug and recruitment to the study stopped in 1995. 19 patients either with locally advanced breast cancer ($n = 12$) or who were elderly, unfit patients with primary breast cancer ($n = 7$) received Onapristone 100 mg/day. Seventeen of the 19 tumours expressed oestrogen receptors (ER) whilst 12 of the 18 tumours tested expressed progesterone receptors (PgR). Tumour remission was categorised by International Union Against Cancer criteria. One patient was withdrawn after 4.5 months while her disease was static. Of the remaining 18 patients, 10 (56%) showed a partial response and 2 (11%) durable static disease (≥ 6 months), giving an overall tumour remission rate of 67%. The median duration of remission was 70 weeks. Transient liver function test abnormalities developed in a number of patients, mainly during the first 6 weeks of treatment. In conclusion Onapristone can induce tumour responses in human breast cancer. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

BREAST CANCER is the most common female malignancy in the western world, with a lifetime risk of at least 1:12 at present. At some point in their disease most patients will receive systemic therapy. The endocrine therapy of choice in postmenopausal or oophorectomised patients is the anti-oestrogen, tamoxifen [1]. Tamoxifen gives a tumour remission rate of approximately 60% in selected patients [2], e.g. those with tumours which are oestrogen receptor (ER) and progesterone receptor (PgR) positive. However, tamoxifen has a partial oestrogen agonistic activity on some tissues and organs. The second-line hormonal agents used in relapse after tamoxifen include aromatase inhibitors (e.g. Aminoglutethamide, Lentaron and, Arimidex) and high-dose progestins (e.g. medroxyprogesterone acetate and megestrol acetate). These drugs are less well tolerated than tamoxifen.

Progesterone antagonists offer a new therapeutic strategy in the treatment of invasive breast cancer. Furthermore, if the molecular studies on the effects of these compounds on breast cancer in animals are confirmed their potential clinical utility may extend back into preneoplastic disease (e.g. atypical ductal hyperplasia).

The progesterone antagonist Onapristone was developed by Schering AG [3, 4]. It was reported to have strong anti-progestational and antitumour activity. Onapristone (ZK 98.299) showed tumour inhibitory effects in several hormone-dependent mammary tumours in animal models. Its antitumour activity is as potent or even more potent than that of tamoxifen or oophorectomy in the MXT mammary tumour of the mouse and DMBA- and NMU-induced mammary tumours of the rat [5, 6]. Although binding to tumour progesterone receptors is a prerequisite for its antiproliferative effects, there is evidence that the mechanism of its antitumour effects does not depend on a classical anti-hormonal mechanism. While the mechanism of action of this new antiprogestin is poorly understood, it has recently been reported that when Onapristone was given to mice bearing

hormone-dependent MXT mammary tumours, in addition to causing tumour regression, the compound caused histological changes suggestive of differentiation to a more benign and mature status [6]. Further *in vivo* work has suggested that the antitumour action of Onapristone is a direct, progesterone-mediated antiproliferative effect at the cell level, probably via the induction of terminal differentiation associated with cell death [5].

The aim of this study was to investigate the clinical and biological effects of this agent as first-line endocrine therapy in patients with breast cancer.

PATIENTS AND METHODS

In September 1994 a phase II study was commenced to assess Onapristone as first-line therapy in postmenopausal patients with primary breast cancer. Patients were eligible to enter the study if they had a locally advanced tumour or were elderly with tumours suitable for endocrine therapy. In all patients endocrine therapy was deemed the initial treatment of choice. A primary goal of the study was to assess by sequential tumour biopsies the effect of Onapristone on tumour biology. The recruitment target was 30 patients. However, owing to the recognition in this and other clinical studies that some patients on Onapristone developed liver function test (LFT) abnormalities, the development of this drug was discontinued and recruitment to the study stopped in 1995. At this time 19 patients had entered the study: 12 patients had locally advanced primary tumours and 7 were elderly patients in whom endocrine therapy was the initial treatment of choice.

When the clinical trial programme on Onapristone was halted all 19 patients were informed of the new data on LFT abnormalities. Since these changes appeared to be transient in all breast cancer patients treated, the 19 patients in this study were offered the option of continuing Onapristone with increased frequency of monitoring LFT measurements or changing to tamoxifen therapy. All patients elected to continue with Onapristone.

This paper reports the clinical response rate and duration of remission in these 19 patients. The minimum follow-up since randomisation was now 24 months and the maximum 32 months. The data on liver function tests in these 19 patients are also reported. These data are particularly important since, unlike the phase II/III studies in patients with metastatic disease, changes in LFT can be attributed to Onapristone rather than to metastatic involvement of liver or bone.

Oestrogen receptors

ER were routinely measured in all pretreatment tumour biopsies by oestrogen receptor immunocytochemical assay (ERICA), as reported previously [7]. Two tumours showed no expression of ER. Of the remaining 17 tumours, four showed ER expression on between 10 and 50% of tumour cells and 13 showed ER expression on between 70 and 100% of tumour cells. PgR was also measured by immunocytochemistry (Abbott Laboratories, Maidenhead, Berkshire, U.K.). 12 patients had PgR-positive tumours and 6 patients had PgR-negative tumours. In the remaining patient PgR status was unavailable.

Therapeutic assessment

Patients were assessed for therapeutic remission using the International Union Against Cancer (UICC) criteria [8].

Since all patients commenced with only a palpable breast tumour the assessment involved measurement of the tumour. The largest diameters of the tumour in two directions were then multiplied together. Similar measurements were made of any regional lymph nodes and the sums of primary tumour and lymph node(s) added. All measurements were carried out by two breast surgeons (JFRR and PCW).

Complete response (CR) was regarded as complete disappearance of the tumour. Partial response (PR) was a reduction of > 50% in the sum of the product of the two largest diameters of palpable tumour (± lymph nodes). Objective response (OR) combines the CR and PR categories. A tumour was classified as static disease (SD) if any change in size ranged between < 50% reduction and < 25% increase in the pretreatment measurements. In all cases (CR, PR or SD) there had to be no new lesions either in the breast or at distant sites. Progressive disease (PD) *de novo* was defined as an increase in tumour size > 25% of the pretreatment value or the appearance of new lesions, or both. PD after a period of response or SD was defined as an increase in tumour size > 25% of the smallest recorded size or the appearance of new lesions, or both.

A further criterion to be fulfilled before patients were classified as CR, PR or SD was the British Breast Group recommendation that tumours had to be in CR, PR or SD after at least 6 months of treatment [9]. This requirement was introduced to prevent reporting short remissions of doubtful clinical benefit. Subsequently, studies have supported this 6-month figure by reporting that patients who show SD for 6 months have a statistically similar survival to patients who show PR or CR. All three groups show a significantly longer survival than the PD group [10–12].

RESULTS

At the 3-month assessment no patient showed PD. Patients' tumours were either in PR ($n = 3$) or in SD ($n = 16$). By 6 months the results were: PD ($n = 6$). SD ($n = 2$) and PR ($n = 10$). One patient discontinued Onapristone after 4.5 months when the tumour was static (see below). The median duration of response for the 12 patients with PR or SD was 70 weeks, compared with 20 weeks for the patients where the tumours showed *de novo* progression. 2 patients remain on Onapristone at a median time of 26 months from entry into the study.

Some patients during therapy developed LFT abnormalities. The number of patients with abnormalities in each test, either before Onapristone treatment or at any time during therapy, is detailed in Table 1. Changes in each of the four liver function measurements are shown over time, and presented in two ways. Figure 1(a)–(d) shows values pretreatment and regular 6-weekly values, as planned in the original protocol. Figure 2(a)–(d) show values pretreatment and at each time point at which blood was obtained during the patient's first year of treatment. Figure 2 reflects the increased frequency of blood sampling in the patients recruited later in the study, when liver dysfunction became known.

Liver function abnormalities appeared mainly during the first 6 weeks of follow-up. In only 3 out of 19 patients did the abnormality in LFT start after 6 weeks with a slight elevation of bilirubin ($n = 1$) (weeks 18 and 24), a 4-fold rise in gamma-glutaryltransferase (GGT) at week 18 ($n = 1$) and a slight elevation of alkaline phosphatase and

GGT ($n = 1$) (week 15 onwards). One patient discontinued Onapristone at 4.5 months owing to rising LFT abnormalities. At the point of discontinuing the drug a further blood test was taken, which subsequently showed that the LFT were starting to fall. Nevertheless, Onapristone was not restarted.

In the 12 patients who had OR or SD 8 were both ER and PgR positive, 3 were ER positive and PgR negative and one

Table 1. Number of patients with liver function test abnormalities

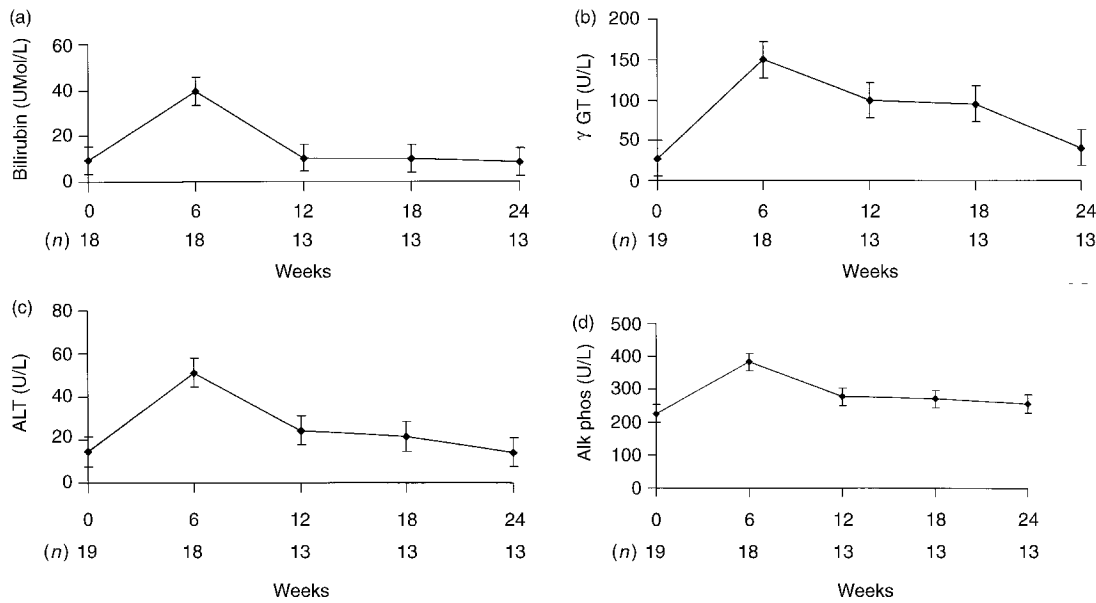|		No. of patients with elevated tests	
	Normal range	Pretreatment	During treatment
Bilirubin	5–17µmol/l	0/18	4/19
Alkaline transferase	5–40 U/l	0/19	12/19
Alkaline phosphatase	80–280 U/l	11/19	18/19
Gamma-glutamyltransferase	10–50 U/l	4/19	14/19

Figure 1. LFT measurements (6 weekly). ALT, alkaline transferase; GT, gamma-glutamyltransferase; Alk, alkaline phosphatase.
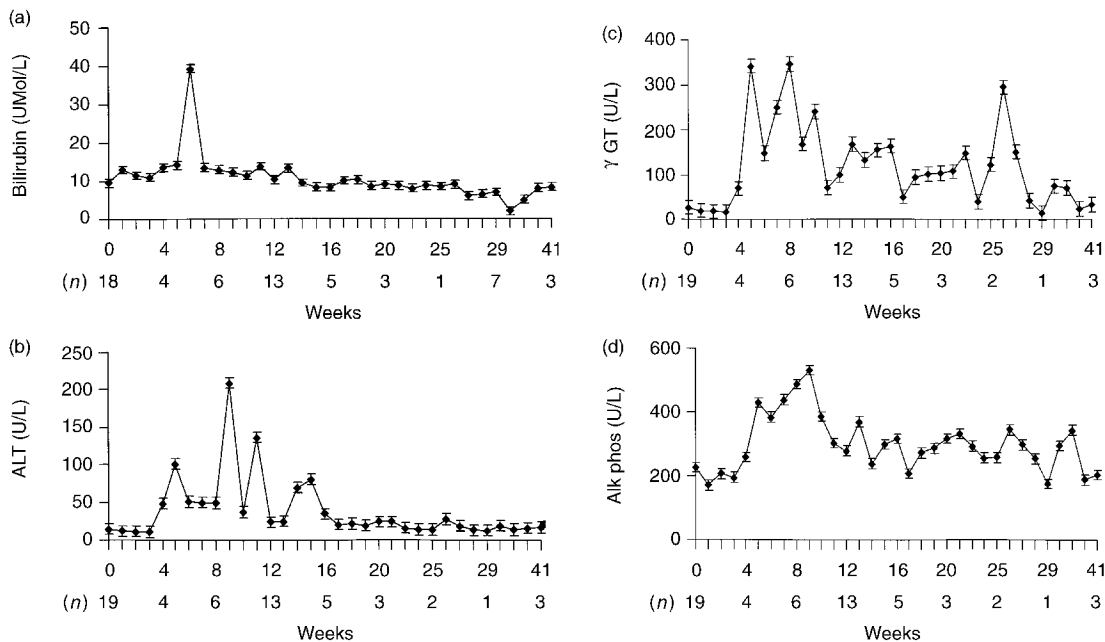

Figure 2. LFT measurements (weekly). For abbreviations, see Figure 1.

PgR unknown was weakly ER positive. In the 6 patients who showed *de novo* progression, 3 were ER and PgR positive, one was ER positive and PgR negative, one was ER negative and PgR positive and one was negative for both receptors.

DISCUSSION

Two-thirds of patients obtained a clinically relevant tumour remission: 10 out of 18 (56%) showed a PR and 2 out of 18 (11%) SD. These figures are at least as good as published remission rates for the anti-oestrogen agent tamoxifen [12–14], synthetic progestogen, megestrol acetate [13–15] and aromatase inhibitors such as aminoglutethamide [16–18] or Lentaron [19] used as first-line endocrine therapies. The high remission rate is in part related to the fact that 17 out of 19 patients were ER and or PgR positive. Similarly, most of the studies referenced above entered only patients with ER-positive tumours or ER status unknown.

It is known that the remission rate is lower to second-line than to first-line endocrine therapy. Recently, 225 patients were reviewed who received both first-line and second-line endocrine therapies; the remission rates were 72% (10% CR + 22% PR + 40% SD) and 53% (3% CR + 8% PR + 42% SD), respectively. In this latter review over 90% of patients received tamoxifen as first-line and megestrol acetate as second-line therapies [20]. Overall, Onapristone appears an effective first-line endocrine agent, with tumour remission rates similar to more established therapies. However, with only 19 patients in the study there were insufficient numbers to draw conclusions about equivalence with other agents.

One or more LFT was elevated in the majority of patients on Onapristone. The abnormalities became apparent in the first 6 weeks of treatment and usually declined thereafter at a steady rate. In 1 patient Onapristone was discontinued and even in this patient the LFT had started to show a downward turn in the sample taken on the day on which therapy was stopped.

The comparison between PgR status and remission needs to be interpreted with caution for the following reasons. In this group of patients, the majority were ER and/or PgR positive. If the same group were treated with an anti-oestrogen such as tamoxifen, not all would respond, despite the presence of ER. In fact, one would expect tamoxifen to induce OR and SD in around 60–70% of ER-positive tumours. In this study 9 out of 14 (64%) patients with PgR-positive tumours showed OR or SD to Onapristone as first-line endocrine therapy.

A recent publication on the progesterone antagonist Mifepristone reported an objective response rate (CR or PR) of 10.7% with a stable disease (duration range 2–17 months) rate of 39.3% [21]. The authors stated that these results were in patients with untreated metastatic breast cancer. However, the majority of patients had received adjuvant hormone therapy (43%) or chemotherapy (32%). This would have influenced the response rates they reported. As noted above, the long-term results have been reported of 250 patients where first- and second-line endocrine therapies were their initial systemic therapies for measurable disease [20], i.e. none had received adjuvant endocrine therapy. Patients received endocrine therapy either for metastatic disease or for local tumours (e.g. elderly, unfit patients or locally advanced disease). The results in the study by Perrault and colleagues appear more reflective of response rates that the present authors have reported to second-line therapy, i.e. 11%

OR + 42% SD [20]. These results are also similar to a recent randomised study of megestrol acetate 40 mg four times daily versus anastrozole 1 mg daily given as second-line endocrine therapy. The OR rates were 12% for both agents and the SD rates were 28% and 30% for megestrol acetate and anastrozole, respectively.

A further point to be considered when comparing results of this study with Onapristone and the study reported by Perrault and colleagues with Mifepristone is the effect of these drugs on the level of oestradiol. In a study by Klijn and colleagues, Mifepristone was reported to cause up to a 5-fold increase in serum oestradiol [22]. Mifepristone in that study was given as second-line therapy and induced an objective response rate of 9% and SD rate of 54%. Onapristone in the present study resulted in no increase in serum oestradiol (data not shown). These latter data are the subject of a separate publication. However, if a 50–90% reduction in serum oestradiol by aromatase inhibitors induces clinical responses, a 5-fold increase by Mifepristone may have an adverse effect on tumour growth. This difference between Onapristone and Mifepristone may be clinically important. Future studies on the effect of pure progesterone antagonists should include an assessment of their effect on sex hormone levels.

The results of this small study of Onapristone as first-line therapy support the preclinical data that Onapristone is a new class of endocrine agent that could have a significant impact on endocrine treatment of breast cancer. From a clinical viewpoint the results of this study support the development of second-generation progesterone receptor antagonists for use in the treatment of breast cancer. Studies are starting to assess whether the sequential tumour biopsies from this study during Onapristone treatment show evidence of the occurrence of tumour differentiation. If confirmed, this would further support preclinical data indicating that progesterone antagonists exert a differentiation effect through a novel mechanism of action. This would further support a development programme of new progesterone antagonists.

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