The clinical efficacy of progesterone antagonists in breast cancer

Walter Jonat, Marius Giurescu, John FR Robertson

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INTRODUCTION

The search for active and safe alternatives to current systemic therapies is one of the main objectives of current breast cancer research. Over the last three decades since the discovery of the estrogen receptor (ER), the development of new endocrine agents has in the main been aimed at either preventing the production of estrogens (e.g. ovarian ablation with gonadotropin-releasing hormone (GnRH) analogues, aromatase inhibition) or blocking their effect by competition for ER (e.g. selective ER modulators (SERMs) and pure antiestrogens). Such developments have focused, indirectly or directly, on the ER as a target for manipulation of tumour growth. This approach is supported by the finding that the response to such therapies is related to the expression of ER by breast tumours.1,3 However, it is also known that response to ‘antiestrogen therapies’ (in the broadest sense) also correlates with the expression of another sex steroid receptor, the progesterone receptor (PgR).1,3

The importance of PgR in breast cancer is controversial. Since the promotor region of PgR contains an estrogen response element (ERE; see Chapter 9), PgR expression may serve as a marker of endocrine dependence, providing indication of a functional PgR.4 As described in Chapter 14, substantial in vitro and in vivo evidence suggests that PgR serves as a biologically important molecule in breast cancer behaviour. Moreover, preclinical studies indicate that blockade of PgR function inhibits proliferation and induces apoptosis (see Chapter 14). Therefore, clinically practical PgR inhibitors have been developed. These are overtly active small molecules that appear to function by binding to PgR and inhibiting pathways downstream of PgR. Two agents, onapristone and mifepristone, have been evaluated in clinical trials, and, as described below, have activity in patients with metastatic disease. Although commercial support for these two agents has recently waned, the concept of PgR inhibition in breast cancer is sufficiently well founded to justify its inclusion in any textbook of endocrine therapy.

Mifepristone (RU38486) was the first progesterone antagonist reported to be useful in the treatment of patients with advanced breast cancer; these were tumours that had developed resistance to prior endocrine therapies.5,6 Prior to these clinical reports, mifepristone and onapristone have been evaluated in clinical trials, and, as described below, have activity in patients with metastatic disease. Although commercial support for these two agents has recently waned, the concept of PgR inhibition in breast cancer is sufficiently well founded to justify its inclusion in any textbook of endocrine therapy.
antiestrogenic treatment were reported to have additive antitumour effects. Treatment with mifepristeone for 3 weeks resulted in decreased expression of ER, although this was slightly less than seen with tamoxifen. In contrast, mifepristeone caused an increase in PgR expression. In the in vivo experiments, mifepristone caused an increase in plasma serum estradiol and progesterone. As noted below, these findings are different to those reported recently using onapristone in a phase II clinical study.

The progesterone antagonist onapristone \(11\beta(4\text{-dimethylaminophenyl})\text{-17\text{o:}-hydroxy-17\text{-(3-hydroxypropyl)}-13\text{\text{-estra-4,9-dien-3-one}}\), was also reported to exhibit tumour-inhibitory effects in several hormone-dependent mammary tumours in animal models. As described in detail in Chapter 14, the main mechanism of action of onapristone appears to be the induction of terminal differentiation, leading to cell death. Its antitumour activity in mouse MXT mammary tumours and rat DMBA- or MNU-induced mammary tumours was as strong as that of tamoxifen or oophorectomy. Toxicological studies carried out in two species (monkey and rat) over a 12-month period did not reveal any changes that could have precluded the use of onapristone in humans. In phase I studies, onapristone was given orally to healthy postmenopausal women in doses of up to 400 mg/day over a period of 14 days. The subjective tolerance of the drug was good. The laboratory parameters did not show any clinically relevant changes, and onapristone entered phase II studies in postmenopausal patients with advanced breast cancer that was tamoxifen-resistant (i.e. as second-line therapy) and a smaller study as first-line therapy in hormone-naive patients. Results of the latter study have been published, but those of the former have not been, to date. This chapter contains the first publication of these data, which will therefore be described in more detail before being reviewed along with the previously published studies.

**ONAPRISTONE**

**Onapristone in tamoxifen-resistant disease (phase II study)**

A non-randomized, open, multicentre phase II study was conducted between December 1991 and May 1995 at 13 sites in Germany and the UK. The study was established to investigate the efficacy of onapristone when given in a dosage of 100 mg/day to postmenopausal patients with advanced breast cancer who had progressed on tamoxifen. The study was also designed to assess patient tolerability and to study the influence of onapristone on the levels of the relevant endocrine parameters (cortisol, androstenedione, estrone, and estradiol). The patient characteristics are described in Table 8.1.

Of the 101 evaluable patients, 1 had a complete remission, 9 had a partial remission, and 39 had stable disease for 3 months or more. This resulted in an overall clinical benefit of 49%. Table 8.2 shows the effect of onapristone on individual sites of disease. The most frequent metastatic site was bone (82 patients), followed by lymph nodes (29 patients), liver (22 patients), skin (20 patients), local recurrence (16 patients), and pleura. A total of 42 patients out of 118 had visceral disease. A complete remission was observed at the site of a local recurrence. Partial remissions were observed in all other major localizations, except pleura.

Out of 10 remissions on onapristone, 8 were achieved in patients who had a benefit from palliative tamoxifen therapy in the form of either remission (3 patients) or stable disease (5 patients) (Table 8.3). Two remissions were registered in patients who had received tamoxifen as an adjuvant therapy. In 2 out of 12 primarily tamoxifen-resistant patients, disease stabilization was registered. No remission was observed in this group.

The response in the group of 33 evaluable patients with PgR-positive primary tumours was 4 patients with partial remission, 15 with stable disease, and 14 with progressive disease.
<table>
<thead>
<tr>
<th>Table 8.1 Patient characteristics</th>
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<tbody>
<tr>
<td><strong>Sample size</strong></td>
</tr>
<tr>
<td><strong>Median age (n = 118)</strong></td>
</tr>
</tbody>
</table>

Menopausal status at diagnosis (n = 118):  
- <2 years postmenopausal: 16  
- >=2 years postmenopausal: 101  
- unknown: 1

ER and/or PgR status at diagnosis (n = 118):  
- ER+/PgR+: 33  
- ER+/PgR: 13  
- ER+/PgR unknown: 7  
- ER+/PgR+: 3  
- ER+/PgR unknown: 6  
- ER-/PgR unknown: 2  
- ER unknown/PgR unknown: 54

ER and/or PgR status at the start of study in patients with lesions accessible to biopsy (n = 18):  
- ER+/PgR+: 7  
- ER+/PgR: 4  
- ER+/PgR unknown: 1  
- ER+/PgR unknown: 5  
- ER/PgR unknown: 1

Previous tamoxifen treatment (n = 118):  
- palliative: 90  
- adjuvant: 28

Relapse-free interval in patients receiving initial palliative treatment (n = 90):  
- <24 months: 12  
- >=24 months: 55  
- unknown: 23

Response to initial palliative treatment (n = 90):  
- complete remission: 5  
- partial remission: 23  
- stable disease: 38  
- progressive disease: 12  
- unevaluable: 8  
- unknown: 4

Duration of previous adjuvant treatment (n = 28):  
- <24 months: 10  
- >=24 months: 12  
- unknown: 6
Table 8.2 Response in Individual sites of disease

<table>
<thead>
<tr>
<th>Localization</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>Bones</td>
<td>2</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>1</td>
</tr>
<tr>
<td>Pleura</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
</tbody>
</table>

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Table 8.3 Response in relation to the results of previous antiestrogen therapy

<table>
<thead>
<tr>
<th>Response to tamoxifen</th>
<th>Response to onapristone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR/PR</td>
</tr>
<tr>
<td>CR/PR</td>
<td>3</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
</tr>
</tbody>
</table>

CR/PR, complete/partial remission; SD, stable disease; PD, progressive disease.

In 8 patients, the PgR status was established in biopsies taken prior to the start of onapristone treatment. The response in this group of patients was 2 patients with partial remission, 2 with stable disease, and 4 with progressive disease. In the group of patients whose tumours were PgR-negative, 2 partial remissions were observed.

The median time to progression was 4 months, and the median time to treatment failure was 3 months. The median time to progression according to response was 11 months (complete or partial remission), 7 months (stable disease), and 3 months (progressive disease).

Onapristone was well tolerated, with the exception of liver function test (LFT) abnormalities. Other laboratory parameters were stable during treatment. Onapristone did not influence body weight or systolic and diastolic blood pressure (data not shown). No systematic changes in the serum concentrations of cortisol,
androstenedione, estrone, and estradiol were observed during the study (data not shown). However, in 20 out of 32 patients with LFTs within normal range at baseline, elevations of one or more parameters - bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), and alkaline phosphatase - were observed. LFTs started to increase after 0.5-1 month of treatment, and reached a maximum after 1 or 2 months. Subsequently, LFTs either stayed unchanged for the rest of the study or returned to normal.

In summary, a clinical benefit for onapristone of 49% compares favourably with results seen with other endocrine agents in patients who have progressed on tamoxifen, including megestrol acetate and aromatase inhibitors.

Onapristone in hormone-naive patients (phase II study)

As the above study of onapristone as second-line endocrine therapy was finishing, a small phase II study as first-line therapy was established. In summary, this study set out to recruit 30 patients, but was stopped after 19 patients had been entered into the trial because the clinical development programme for onapristone was halted. Nonetheless, the agent appears to be active in this setting.

Of the 19 patients entered into the study, one was withdrawn after 4.5 months owing to marked elevation in the patient’s LFTs. At this time, the patient had stable disease. In the remaining 18 patients, 10 achieved partial remission, 2 had durable stable disease (>24 weeks), and 6 had de novo progression. Thus, the overall clinical benefit was 66%. As previously reported, the majority of patients had hormone-receptor-positive tumours. Ten patients were ER-positive/PgR-positive, of whom 7 achieved partial remission, 1 had stable disease, and 2 had de novo progressive disease. Six patients had ER-positive/PgR-negative tumours, of whom 2 achieved partial remission, 2 had stable disease (1 of whom was the patient withdrawn for LFT elevations after 4-5 months), and 2 had progressive disease. Two patients had ER-negative/PgR-negative tumours, both of whom showed de novo progression.

Overall, the clinical benefit rate of 66% (12 of 18 patients) is similar to the published remission rates for the antiestrogen tamoxifen, the synthetic progestin megestrol acetate, and aromatase inhibitors such as anastrozole.

There was no change in serum estradiol during the first 6 months (data not shown). LFT elevations were noted in the majority of patients. These were initially detected at 6 weeks, when the first on-treatment blood samples were taken. Later in the study, when LFT measurements were performed weekly, the elevations in LFTs were detected from weeks 1-2 onwards.

Onapristone (two doses) versus megestrol acetate (phase III study)

Given the favourable phase II results, a comparative trial of two doses of onapristone (50 mg/day and 100 mg/day) versus megestrol acetate was started. In view of the LFT results in the phase II studies, early review was carried out of the LFT results in this phase III study. Elevations of LFTs occurred with a higher incidence in the two onapristone arms, without clear signs of dose dependence. Subsequently, the development of onapristone was terminated by the sponsor. The mechanism of onapristone-associated liver toxicity is not fully understood. Taking into account (1) that LFT alterations were transient in a number of patients despite continued treatment, (2) that dose level, duration of treatment, and total exposure did not appear to play a role, and (3) onapristone’s failure to elicit comparable effects in animals, the likely mechanism could be an idiosyncratic reaction to onapristone rather than a direct hepatotoxic effect.

Since no comparative trials with onapristone were completed, the potential of this drug in relation to current endocrine therapies could
not be conclusively evaluated. Nevertheless, the level of clinical activity demonstrated by onapristone in the phase II studies indicated that progesterone antagonists have therapeutic potential in the treatment of breast cancer and supported the earlier studies of mifepristone.

MIFEPRISTONE

Mifepristone in tamoxifen-resistant disease (phase II studies)

The first clinical report of a progesterone antagonist in patients with breast cancer was of mifepristone as second-line therapy in advanced disease. In the study by Romieu and colleagues, 3 out of 22 patients achieved partial remission, with a further 9 showing stable disease. Klijn and colleagues reported that 1 patient out of 11 achieved partial remission, with a further 6 showing stable disease. Together, these phase II studies reported on 33 patients with advanced breast cancer who were treated with mifepristone. Overall, 4 out of 33 patients (12%) achieved partial remission, with a further 15 (46%) showing stable disease. These results for second- and/or third-line endocrine therapy are consistent with the literature, and are similar to the results obtained with onapristone that have been described above.

Mifepristone in hormone-naive breast cancer (phase II study)

One further study of mifepristone in advanced breast cancer was reported by Perrault and colleagues. A 10.7% objective response rate (complete plus partial remissions) and a 39.3% stable disease rate was reported for what the authors described as patients with untreated metastatic breast cancer. However, it should be noted that 43% of the patients had received a prior endocrine agent as adjuvant therapy, while 32% had received adjuvant chemotherapy. These prior systemic therapies, albeit as adjuvant treatment, would have influenced the response rates when the patients received mifepristone for metastatic disease. In reality, therefore, mifepristone in this study was, for many of the patients, being used as a second endocrine agent on failure of adjuvant endocrine therapy, and the results seem more reflective of response rates reported for second-line endocrine therapies.

It should also be noted that mifepristone has been reported to cause an increase in serum estradiol. In contrast, onapristone caused no such increase. While the significance of this remains to be established, it is known that a 50-90% decrease in serum estradiol by aromatase inhibitors is associated with objective remissions. Whether the increases in serum estradiol seen with mifepristone have any effect on tumour growth is an intriguing but as yet unanswered question.

SUMMARY

The progesterone antagonists onapristone and mifepristone have been used in clinical studies in advanced breast cancer. Onapristone entered phase II clinical trials as both second-line and first-line endocrine therapy. Only the smaller first-line study has thus far been published, and therefore this is the first report of the larger phase II study of onapristone as second-line therapy. In this trial, 118 postmenopausal patients with systemic progressive disease resistant to antiestrogens received 100 mg/day onapristone orally. One hundred and one patients were evaluated for response, with the following results: 1 complete remission, 9 partial remissions, 39 cases of stable disease, and 52 cases of progressive disease. The median time to progression was 4 months. These findings, along with published phase II studies using another progesterone antagonist, mifepristone, which reported similar clinical efficacy, indicates that progesterone antagonists may have therapeutic potential in the treatment of breast cancer.

Mifepristone is currently being investigated.
in combination with tamoxifen rather than as a single agent. The clinical development of onapristone has been stopped by the sponsor. Although clinically onapristone seemed to be well tolerated, its administration was associated with elevation of liver function tests in a significant number of patients. Nevertheless, the studies of antiprogestins to date have confirmed that this class of endocrine agent has clinical activity, providing impetus to search for newer antiprogestins.

REFERENCES

20. Ingle JN, Creagan ET, Ahmann DL et al.


