Abstract. Recent experimental observations, showing the potential role of prolactin (PRL) as a tumor growth factor for prostate cancer and the unfavourable prognostic significance of enhanced chromogranin-A-secreting neuroendocrine cell proliferation, could contribute to a better understanding of the mechanisms responsible for the occurrence of hormone-resistant prostate cancer. Moreover, it has been shown that tamoxifen, which consistently exerts estrogenic activity in males, may inhibit prostate cancer cell proliferation in experimental studies. At present, there are no clinical data in humans. This preliminary phase II study was planned in an attempt to evaluate the therapeutic efficacy of tamoxifen in hormone-refractory metastatic prostate cancer. The study included 14 consecutive metastatic prostate cancer patients, who had progressed under the classical endocrine therapy with LHRH-analogs and/or anti-androgens. Patients received the same treatment plus tamoxifen at 20 mg/day orally. A decline greater than 50% in prostate-specific antigen (PSA) levels occurred in 4/14 (29%) patients within the first 2 months of therapy, with a median duration of 5 months. Mean pretreatment levels of PRL were significantly higher in responder patients than in those who progressed. Moreover, abnormally high pretreatment levels of PRL were found in 5/14 (36%) patients. The percent of clinical responses observed in patients with pre-treatment hyperprolactinemia was significantly higher than that found in patients with normal pre-treatment PRL concentrations. Finally, a significant decline in mean PRL levels upon tamoxifen therapy occurred only in the responder patients. This preliminary study seems to justify further clinical research to confirm the potential efficacy of tamoxifen in the treatment of hormone-refractory prostate cancer and to identify possible parameters, which may predict the response to treatment.

Materials and Methods

The major obstacle in the treatment of metastatic prostate cancer is the occurrence of androgen hormone resistance. Recent experimental observations have shown that the hormone-independency of prostate cancer is mainly due to the proliferation of neuroendocrine cells, which are characterized by endocrine-refractory growth (1), and whose enhanced activity may be documented by the increase in the blood concentrations of their specific marker, chromogranin-A (Cg-A) (2). In addition, it has been shown that androgen-independent prostate cancer cells may be stimulated by prolactin (PRL) (3). PRL could thus represent a potential growth factor for prostate cancer (4), namely for androgen-independent cancer cells. Moreover, PRL blood levels may be abnormally high in metastatic prostate cancer patients (5), that is in those with hormone-refractory neoplasm. On the other hand, estrogen-receptor modulators, including tamoxifen and raloxifen (6), have been proven to inhibit prostate cancer proliferation through an androgen-independent pathway (7, 8). In addition, increased estrogen-receptor expression has been found to be associated with prostate cancer progression and with the onset of hormone resistance (9). Within the group of estrogenic substances, it is known that tamoxifen may exert both agonist and antagonist estrogenic effects, depending on the blood estradiol concentrations (6), while in males it exerts only an estrogenic effect. Despite these observations, at present there are no clear clinical data regarding the possible therapeutic efficacy of tamoxifen in hormone-refractory prostate cancer. The present preliminary phase II study was performed in an attempt to analyze the possible therapeutic efficacy of tamoxifen in hormone-resistant metastatic prostate cancer.

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experimental protocol was explained to each patient and written consent was obtained. Patients with a previous history of thromboembolic events were excluded from the study. Hormone resistance was established on the basis of a progressive increase in PSA serum levels in three successive measurements at 1-month intervals. Patients were treated with the original therapy of LHRH-analogs and/or anti-androgens, in association with tamoxifen at an oral dose of 20 mg/day every day until disease progression. Patients were considered to be evaluable when they had been treated for at least 2 consecutive months. Clinical response was evaluated according to WHO criteria, and on the basis of changes in PSA serum concentrations. Moreover, to investigate the possible influence of PRL on the clinical response, serum levels of PRL were measured in venous blood samples collected in the morning before the onset of treatment and at 1-month intervals until disease progression. Moreover, in 7/14 patients, Cg-A serum levels were also measured before the onset of treatment. PRL and Cg-A serum concentrations were measured with an enzyme immunoassay, using commercially available kits. Normal values (95% confidence limits) obtained in our laboratory in healthy male subjects were below 21 ng/ml for PRL and below 70 ng/ml for Cg-A. The data were statistically analyzed by the Chi-square test, the Student’s t-test, the analysis of variance and the coefficient of correlation, as appropriate.

Results

Patient clinical characteristics are provided in Table I. The treatment consisted of LHRH-analog, anti-androgens and tamoxifen in 13/14 patients, while the last patient received tamoxifen alone. All patients were evaluable for clinical response. A decrease greater than 50% in PSA serum levels was achieved within the first 2 months of therapy in 4/14 (29%) patients, whereas a progressive increase in PSA values occurred in the other 10 patients, including the patient who received tamoxifen alone. The median duration of response was 5 months (range 3-8 months). Abnormally high PRL levels before the onset of treatment were observed in 5/14 (36%) patients. A PSA decline greater than 50% was significantly higher in patients with pre-treatment hyperprolactinemia than in those with PRL levels within the normal range (3/5 (60%) vs. 1/9 (11%), respectively, \( p<0.05 \)). Mean PRL levels observed in patients with response or progression before the onset of treatment and after 2 months of therapy are illustrated in Figure 1.

The mean pre-treatment PRL levels were significantly higher in patients with response than in those who progressed on therapy (\( p<0.05 \)). Moreover, the PRL mean concentrations significantly decreased on treatment in responder patients (\( p<0.025 \)), whereas they increased in progressing patients, without, however, statistically significant differences with respect to the pre-treatment values. Abnormal pre-treatment Cg-A values were observed in 4/7 (57%) patients. Moreover, the mean serum levels of Cg-A were significantly higher in patients with normal PRL pre-treatment concentrations than in those with cancer-related hyperprolactinemia (279±36 vs. 86±21 ng/ml, X±SE, \( p<0.01 \)). In addition, pre-treatment Cg-A

Table I. Clinical characteristics of 14 hormone-resistant metastatic prostate cancer patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Median age (years)</td>
<td>66 (55-82)</td>
</tr>
<tr>
<td>Median performance status (Karnofsky’s score)</td>
<td>80 (60-100)</td>
</tr>
<tr>
<td>Metastasis sites</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>9</td>
</tr>
<tr>
<td>Bone + Nodes</td>
<td>2</td>
</tr>
<tr>
<td>Bone + Lung</td>
<td>2</td>
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<tr>
<td>Bone + Nodes + Lung</td>
<td>1</td>
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Figure 1. Tamoxifen efficacy in hormone-resistant metastatic prostate cancer patients in relation to PRL pretreatment levels and its changes after 2 months of therapy.
concentrations were significantly lower in patients whose PSA decreased after therapy, than in those who progressed (138±33 vs. 314±41 ng/ml, p <0.05). However, no statistically significant correlation was observed between PRL and Cg-A pre-treatment concentrations (p=0.09).

No tamoxifen-related toxicity occurred. On the contrary, a complete relief of pain due to bone metastases was achieved in 3/4 (75%) responder patients. Finally, tamoxifen was effective in the treatment of pain due to anti-androgen-induced gynecomastia in 4/6 (67%) patients presenting that symptom.

Discussion

The results of this preliminary study indicate that the estrogen-receptor modulator tamoxifen may be potentially effective in the treatment of hormone-resistant metastatic prostate cancer, and constitute, to our knowledge, the first clinical evidence of the potential therapeutic activity of tamoxifen in metastatic prostate cancer patients, refractory to the classical endocrine therapy with anti-androgens and LHRH-analogs. However, the small number of patients does not allow conclusions to be drawn regarding which subset of patients may obtain benefits from tamoxifen therapy. Nevertheless, according to the biological results of this study, it seems that tamoxifen efficacy may be greater in patients with prostate cancer-related hyperprolactinemia. On the contrary, evidence of abnormally high concentrations of Cg-A before the onset of treatment may be associated with a lack of response to tamoxifen treatment. In any case, further studies in a greater number of patients are necessary in order to better define the relationship between Cg-A and PRL concentrations in hormone-refractory metastatic prostate cancer. According to the preliminary results of this study, the existence of two different mechanisms, depending on enhanced secretions of either PRL or Cg-A, could be responsible for endocrine resistance in metastatic prostate cancer patients. PRL could act as a potential growth factor for prostate cancer, whereas the abnormally high levels of Cg-A simply reflect increased neuroendocrine cell proliferation (1-4). Therefore, further studies, which simultaneously monitor PRL and Cg-A concentrations after treatment, are necessary to confirm the potential efficacy of tamoxifen in the treatment of hormone-resistant metastatic prostate cancer, and to identify possible biological markers which may predict the efficacy of the treatment.

With regard to tamoxifen efficacy and PRL secretion, the results of the present study do not allow us to affirm that decreases in PRL levels after tamoxifen administration in responder patients depend on a direct inhibitory effect of tamoxifen itself on PRL secretion. On the contrary, since PRL may be directly produced by cancer cells as an autocrine secretion (1-4), the PRL level decline observed only in the responder patients could simply be the consequence of the inhibitory effect of tamoxifen on prostate cancer cell proliferation and biological activity. This hypothesis could explain the complete lack of endocrine effects of tamoxifen on PRL secretion in cancer patients who received no benefit from this new endocrine therapeutic approach.

References