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Hormonal Therapy for Metastatic Renal Cell Carcinoma Combined Androgen and Provera Followed by High Dose Tamoxifen

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The purpose of this phase II study was to determine the effectiveness of hormonal therapy with combined high dose androgen and provera or tamoxifen in patients with advanced renal cell carcinoma. 30 patients with metastatic renal cell carcinoma received testosterone propionate 100 mg intramuscularly (i.m.) 5 times weekly plus provera 400 mg (i.m.) twice weekly until disease progression developed. 20 patients, most of whom had previously failed to respond to androgen and provera, received tamoxifen 100 mg/m² daily. Of the 30 patients treated with androgen and provera, 3 (10%) developed partial responses of brief duration. 2 of 20 patients (10%) experienced tumour response with tamoxifen, one instance of complete disappearance of pulmonary metastases in a patient whose primary tumour was questionably persistent at post mortem and another case demonstrating disease stability. Combined hormonal therapy offers very little therapeutic advantage in advanced renal cell carcinoma. Tamoxifen, in high dose, exerts anti-tumour effects in a small cohort of cases.
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INTRODUCTION

FOR MANY malignant diseases major changes in outcome have resulted from extensive trials with antineoplastic agents including newer hormonal agents, cytotoxic drugs, and biological response modifiers, as well as the innovative use of combined therapeutic modalities. Renal cell carcinoma, however, remains a neoplastic disease with minimally effective systemic therapy, most recently interleukin-2 or combinations of biological response modifiers have achieved clinical importance [1, 2].

Hormonal therapy, because of its low toxicity, has been a durable approach to the management of renal cell cancer. Bloom and Wallace reported the initial clinical studies with androgen and progestational agents over 25 years ago [3]. Since then the response rates have fluctuated between 0 and 20%, and are generally 10% or less [4, 5]. In the past two decades several groups have demonstrated the presence of oestrogen and progesterone receptors in renal tumour tissue [6, 7]. There is little correlation between the presence of receptors and response to hormonal therapy. Since the binding affinity of the receptors is considered weak, it is postulated that large doses of hormones might be required to exert significant antineoplastic effects [6].

This prospective study was initiated to determine whether the simultaneous use of two hormones with known antitumour effects in renal cell cancer would exert additive response and whether administration of high dose antioestrogen could yield antineoplastic effects in renal cell cancer.

PATIENTS AND METHODS

Patients

30 patients with a histological diagnosis of renal cell carcinoma were eligible for the study (Table 1). None had received prior chemotherapy, hormonal treatment nor radiotherapy to the primary tumour site. 15 patients had had prior nephrectomy. There were 29 males and 1 female. The median age was 62 with a range of 47 to 88 years. Patients had evidence of measurable progressive disease by palpable masses, X-ray, computer tomography (CT) and/or bone scan. The median time from diagnosis to treatment for all patients was 6 months with a range from 1 to 60 months. Before therapy patients were evaluated by history, physical examination, complete blood counts, SMA 20, chest X-ray, CT scans of the abdomen, chest, brain and bone scans.

Treatment schedule

Therapy with androgen and provera was as follows: testosterone propionate was administered as 100 mg intramuscularly (i.m.) 5 times weekly; provera was given simultaneously, 400 mg

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Table 1. Patients' characteristics: hormonal therapy

	Number
No. of patients	30
Median age (range)	62 (47–88)
Sex	
Male	29
Female	1
Median time from diagnosis (range)	6 months (1–60)
Site of metastases	
Lung	17
Bone	17
Liver	10
Lymph nodes	6
Brain	4
Soft tissue	4
Prior nephretomy	15

i.m. twice weekly. Both hormones were continued until disease progression occurred. Assessments of disease were made every 4 weeks unless clinical changes developed earlier.

Four weeks after cessation of androgens and provera, oral tamoxifen, 100 mg/m^2 daily was initiated. Patients who developed profound clinical deterioration on androgen and provera did not receive tamoxifen. Patients who did receive tamoxifen were continued on therapy until disease progression was evident.

Response criteria

Complete response is defined as disappearance of measurable disease for at least 4 weeks. Partial response is defined as 50% or greater reduction in the sum of the products of all measurable disease. Stable disease represents no evidence for progression of individual lesions nor appearance of new lesions for at least 4 weeks as well as regression of less than 50% in evaluable lesions. Progression of disease is defined as the appearance of new lesions and/or increase in size of measurable disease.

RESULTS

The results are shown in Table 2. Of 30 patients treated with androgen and provera, there were three partial responses (10%). The median duration of treatment was 2 months with a range of 1 to 9 months; responses were 3, 4 and 9 months in duration. The sites of disease in cases who responded were pulmonary nodules in 2 patients and a lytic bone lesion which demonstrated recalcification in the third patient. No significant toxicity developed in the androgen and provera treated patients. A rise of 8–10 points in haematocrit values was noted in 4 cases.

Table 2. Responses to hormonal therapy

	Androgen and provera	Tamoxifen
No. of patients	30	20
Complete response	0	0
Partial response	3	1
Stable disease	0	1
Progressive disease	27	18
Median survival		
All cases (range)	15 months (1–120)	
Responders	12 months	

There were 20 patients who entered the trial with high dose tamoxifen. The median duration of treatment was 2 months with a range of 1–16 months. There was one response and 1 patient who experienced stable disease. Both cases were of particular interest and are described below.

A 62 year old man was found to have pulmonary nodules which were biopsied to reveal metastatic renal cell carcinoma. The primary tumour was identified by arteriogram. Two months after beginning high dose tamoxifen the nodules could not be identified by X-ray. The tamoxifen was discontinued 1 month later, followed by the reappearance of the pulmonary nodules. Reinstitution of high dose tamoxifen resulted in complete disappearance of the pulmonary nodules. The patient, who had had known coronary artery disease of several years duration, died of cardiac arrest, and post mortem failed to reveal pulmonary metastases. The primary tumour showed extensive fibrosis, necrosis and some foci of tumour.

A 53-year-old man who had had nephrectomy 2 years before the appearance of pulmonary metastases developed regression of the lung lesions on high dose tamoxifen. The regression was less than 50% of measurable lesions. Inadvertently, the dose of tamoxifen was reduced to 10 mg twice a day. The lung nodules then increased in size. When the higher dose was again started, regression of the pulmonary metastases recurred for a period of 4 months.

DISCUSSION

In this study the simultaneous use of androgen and provera in high doses did not improve the effectiveness of either agent singly. The overall response rate was 10% with partial responses of brief duration. Nevertheless, in one instance, recalcification of bone metastases was observed, a distinctly unusual occurrence with other forms of treatment for this disease.

The doses of androgens and provera utilised in this trial were those introduced by Bloom and Wallace [3]. In our earlier study these were found to be capable of inducing tumour regression in cases of advanced renal cell carcinoma [9].

The use of high dose tamoxifen in a smaller group of 20 cases, suggests that this agent has only moderate antineoplastic effects in renal cell carcinoma. 1 patient had complete resolution of pulmonary metastases. This was clearly related to the tamoxifen therapy since the metastatic disease, documented by biopsy, recurred when the drug was stopped, and resolved when the tamoxifen was reinstituted. Moreover, this developed in a patient who had not had nephrectomy. This patient is classified as a partial response since there were foci of tumour detected at post mortem in the kidney, despite the absence of detectable pulmonary metastases. In the setting of extensive fibrosis and necrosis of the primary tumour, it is possible that these foci were not viable tumours. Nevertheless, it seems appropriate to apply stringent standards, and consider this a partial response. Another observation of interest was the relationship of the response to the dose as noted in the second case. At 100 mg/m^2 a reduction in the pulmonary nodules developed, but following inadvertent dose reduction to 10 mg/m^2 the lung nodules increased. With a return to the higher dose level, the lung nodules again regressed.

A number of earlier reports on the use of tamoxifen in renal cell carcinoma employed low doses. In these trials a response rate of 0–7% is cited [9–11]. In a series of 15 patients given 80 mg daily, 2 showed partial response [12]. From the present experience, for some patients a high dose may be important

to achieve regression, although the overall response rate we observed is not appreciably different from the literature experience.

The results from tamoxifen are similar to those obtained with androgen and provera, although the patients who responded to tamoxifen had not previously responded to androgen and provera.

Systemic therapy for advanced renal cell carcinoma rarely yields significant benefit. Extensive trials with cytotoxic agents, singly or in combination indicate that this neoplastic disease is refractory to the majority of agents [13]. Biological response modifiers, the interferons, interleukin-2 with or without activated leucocytes, and combinations of these materials, show occasional striking results, frequently achieved with debilitating toxicities [14–17].

Innovative therapeutic strategies are needed for this disease. While trials of warfarin and cimetidine and infusional floxuridine are examples of such attempts, the usual outcome is a decline in the response rate upon repetitive study [18–20].

Whether the response to hormonal therapy in renal cell carcinoma is mediated through endocrine mechanisms is unclear. The response rate is much lower than the observed occurrence of receptors in tumour tissue, and the correlation of response with the presence of receptors is poor [21].

There is laboratory data in animal systems suggesting that hormones are involved in renal carcinogenesis [22]. Tamoxifen has been shown to inhibit oestrogen induced renal carcinogenesis in male Syrian hamsters, the model upon which the initial trial of hormonal therapy of renal cell cancer was based [23]. In this animal system, tamoxifen did not influence the production of DNA adducts, but was growth inhibitory. It seems likely that tamoxifen did not *per se* inhibit tumour induction, but possibly exerted antineoplastic effects by another mechanism.

There is evidence that tamoxifen possesses the capability of inhibiting growth factors which are expressed in normal and neoplastic renal tissue, namely transforming growth factor alpha and epidermal growth factor [24, 25]. A more important function may be the enhancement of the action of transforming growth factor beta, a growth inhibitor [26]. In human breast cancer, tamoxifen is also known to reduce circulating levels of insulin-like growth factor [27] although the significance of this observation to renal cell carcinomas is not known.

Other pharmacological properties of tamoxifen include inhibition of protein kinase and the ability to reverse resistance to some cytotoxic agents [28, 29]. This suggests that incorporation of tamoxifen into trials with cytotoxic agents may prove beneficial in renal cell carcinoma.

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