immediate cause of death. Assuming heterogeneity of the cytotoxic effects of chemotherapy could give rise to behaviour compatible with the findings of our study, whereby relapse is a phenomenon associated with relatively large numbers of drug resistant cells while death is sometimes due to relatively small colonies of drug sensitive cells causing the failure of a vital organ.

The two hypotheses, that proliferation rates differ between tumour cells sensitive and resistant to cytotoxic therapy and that chemotherapy has heterogeneous cytotoxic effects in different organs of the body, although biologically plausible, are rather speculative. Data from the present study are insufficient to test either. However, our findings do indicate that an over simplistic view of the effects of chemotherapy can be misleading.

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Lack of Therapeutic Efficacy of Tamoxifen in Advanced Renal Cell Carcinoma

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In the present study, we treated a total of 62 patients with advanced renal cell carcinoma with high-dose tamoxifen (100 mg/m²/day). Patients were treated in the outpatient setting, and were evaluated 8–12 weeks after initiation of therapy or sooner, when clinical disease progression was evident; a total of 15 patients were seen at short regular intervals for evaluation of clinical and laboratory parameters. Of these 62 patients, 59 were evaluable for treatment response, survival and systemic toxicity. One partial remission was achieved (1.7%; 95% confidence interval, 0.04–9.09%), response duration was 3 months. 10 patients presented with stable disease, for a median duration of 4.0 months, and 48 patients exhibited disease progression upon and after therapy. Systemic toxicity was significant; severe fatigue occurred in 5% of patients, and moderate anaemia, dyspnea, alopecia and malaise in almost 20% of patients. Antineoplastic efficacy of tamoxifen at this dosage in this cohort of patients was at best marginal and well in the range associated with the occurrence of spontaneous remissions. Toxicity was substantial, and it was not balanced by therapeutic benefit. This is consistent with the known lack of therapeutic efficacy of endocrine therapy in advanced renal cell carcinoma.
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INTRODUCTION

THE OVERALL prognosis of patients with advanced renal cell carcinoma is poor. While spontaneous regression of a metastatic disease has been reported to occur in 0.5–5% of patients [1], more than 70% of patients succumb to their tumour within 1 year of diagnosis of metastatic renal cancer [2].

Based on experimental tumours in Syrian golden hamster models [3], hormonal manipulations were felt to be justified in advanced renal cancer patients. Patients were treated with a wide variety of hormone agonists and antagonists, such as corticosteroids, progesterones and antioestrogens. As Hrushesky and Murphy noted [4], with the application of stricter response criteria to study populations, response rates of endocrine therapy decreased from 17–33% between 1967 and 1971 to 2% between 1971 and 1976 [5].

Tamoxifen is a non-steroidal antioestrogen which is successfully administered in breast cancer patients [6]. Some breast cancer cells are known to possess oestrogen receptors. However, on renal cell carcinoma cells, previously documented oestrogen

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binding was ascribed to high levels of non-specific binding [7, 8].

A number of other mechanisms of action have been suggested for tamoxifen. These include interactions with specific antioestrogen binding sites [9], inhibition of protein kinase C [10], tamoxifen-induced release of secondary cytokines such as transforming growth factor-β [11], modulation of natural killer cell activity [12, 13] and direct cytotoxicity against breast cancer cells [14].

Given previous reports suggesting a clinical efficacy of tamoxifen in advanced renal cell cancer, we performed a phase II study to definitively assess the therapeutic potential of this treatment. Here, we report on 62 patients treated with high-dose tamoxifen (100 mg/m²/day). 59 patients were evaluable for treatment response, long-term survival and for tamoxifen-induced adverse effects as relevant parameters of palliative tumour therapy.

PATIENTS AND METHODS

Patients

Between May 1990 and March 1992, 62 patients were treated with high-dose tamoxifen. All patients had measurable, histologically confirmed advanced renal cell cancer. 3 patients were lost to follow-up. 59 patients were evaluable for treatment response and toxicity, 15 patients were seen at biweekly intervals and assessed for haematological and serological parameters. Irrespective of surgery and limited field radiation therapy, 27 patients were previously untreated; 32 patients were pretreated with a variety of immunotherapy regimens, as shown in Table 1.

*Table 1. Patient characteristics**

Total number	62
Number evaluable	59
Sex	
Male	40
Female	19
Age (years)	
Median	59
Range	33–75
ECOG performance score	
0	20
1	31
2	8
Pretreatment	
Tumor nephrectomy	56
Relapse surgery	16
Local radiotherapy	25
Chemotherapy	8
Cyclophosphamide	1
Mafosfamide	4
Vinblastine	3
Immunotherapy	32
IFN-α	1
IFN-α/VBL	6
IFN-α/IL-2	17
IFNα/IL-2/5-FU	6
Tumour vaccines	2

IFN-α, Recombinant human interferon-alpha; IL-2, recombinant human interleukin-2; VBL, vinblastine; 5-FU, 5-fluorouracil.
*3 patients were lost to follow-up. 59 patients were evaluable in this study; all patients had histologically confirmed advanced renal cell cancer; 27 patients received tamoxifen as first systemic therapy, whereas 32 patients were pretreated with various immunotherapy regimens.

Therapy

All patients received oral tamoxifen at 100 mg/m² in three divided doses per day. Patients were evaluated at 2–3-month intervals, unless clinical evidence of disease progression required earlier cessation of therapy.

Response and toxicity evaluation

Objective response was defined as a decrease of at least 50% in the product of the longest perpendicular diameters of metastatic lesions measurable by radiographic or clinical means. Progressive disease (PD) was defined as more than a 25% increase in the product of perpendicular diameters or the appearance of new lesions. Response duration was calculated from the onset of therapy to date of progression or death.

Toxicity was evaluated at regular intervals and scaled according to a grading system adapted from the WHO. Haematological and serological studies included complete blood counts, electrolytes, liver function tests, serum lipid levels, total protein and electrophoresis, fibrinogen, creatinine, urea nitrogen and uric acid.

Statistical analysis

Laboratory parameters before and during therapy were compared using a Wilcoxon's matched-pairs signed-ranks test to assess the pair-to-pair variability of the patients' data. All P values < 0.05 were considered significant.

RESULTS

Therapeutic effects

59 patients were evaluable for treatment response. As shown in Table 2, 1 patient [objective response rate, 1.7%; 95% confidence interval (CI), 0.04–9.09%] achieved a partial remission (PR) with a duration of 3 months; 10 patients (16.9%) had stable disease upon therapy with a median duration of 4 months (range, 2+–6 months); 48 patients (81.4%) presented with PD.

Overall median survival from diagnosis of metastatic disease was 18 months (range, 3–41+ months); it was 19.5 months in immunotherapy pretreated patients, and 14.5 months in previously untreated patients. Median survival from start of systemic therapy was 14 months (range, 3–33+ months) in immunotherapy pretreated patients, and 7 months (range, 2–36+ months) in patients receiving tamoxifen as first-line therapy.

Systemic adverse effects

The overall systemic toxicity of tamoxifen was mostly moderate, and it did not require additional medical intervention. Thus, grade III toxicity was limited to severe malaise occurring in 3 patients. Grade II nausea/vomiting, anorexia, dyspnea and alopecia developed in 4, 5, 9 and 10 patients, respectively. 2 female patients died after the onset of tamoxifen therapy with clinical symptoms of pulmonary embolism. Several patients reported reduced libido and/or vaginal discharge, occasionally associated with irregular menses, but these symptoms were judged not to be clearly therapy-induced in cancer patients. There was no obvious tamoxifen-related ocular impairment in these patients.

Table 2. Sites of disease and response to tamoxifen (100 mg/m²/day)

Site	Response* PR	SD	PD	Total
Lung	1	6	42	49
Liver	—	2	10	12
Local relapse	—	1	13	14
Lymph nodes				
Abdominal	—	—	15	15
Mediastinal	—	1	16	17
Peripheral	—	—	7	7
Skin/soft tissue	1	—	5	6
Pleura	—	1	5	6
Pancreas	—	—	2	2
Bone	—	2	19	21
Brain	—	1	10	11
Other†	—	—	3	3
Total patients	1 (1.7%)	10 (16.9%)	48 (81.4%)	59 (100%)

PR, Partial remission; SD, stable disease; PD, progresssive disease.
*Response duration was 3 months for the PR patient; median progression-free interval was 3 months (range, 2+–6) in previously untreated SD patients, and 4 months (range, 2–6) in immunotherapy pretreated SD patients.
†Kidney in 2 patients, thyroid gland in 1 patient.

Haematological toxicity

Grade II anaemia was noted in 8 patients, with the mean haemoglobin level in all patients decreasing from 127 ± 20 g/l (range, 91–161 g/l) to 124 ± 21 g/l (range, 88–163 g/l; $P = 0.62$) when compared with baseline. The platelet count fell from 316 ± 115 thrombocytes/nl to 254 ± 62 thrombocytes/nl after therapy ($P = 0.14$). There were no consistent changes of total leukocyte and neutrophil counts.

Serological toxicity

Grade I hepatoxicity, notably increases in transaminases and alkaline phosphatase serum activity, was observed in 8 patients. Serum aspartate aminotransferase levels significantly increased upon therapy from 7.7 ± 4.2 U/l (range, 4–20 U/l) to 17.2 ± 16.4 U/l (range, 5–67 U/l; $P = 0.0034$) when compared with baseline; concomitantly, serum cholinesterase activity decreased from 5.3 ± 1.4 kU/l to 4.1 ± 1.6 kU/l ($P = 0.011$). There was a trend to lower total protein (67.4 ± 8.1 g/l compared with baseline levels of 71.3 ± 7.4 g/l; $P = 0.059$) and serum cholesterin levels (6.0 ± 14.1 mmol/l compared with baseline of 6.8 ± 1.4 mmol/l; $P = 0.21$) after therapy. Serious serum electrolyte imbalances did not occur, except for marked hypercalcemia in a patient with no bone lesions.

Table 3. Systemic toxicity upon tamoxifen therapy (100 mg/m²/day)

Side-effect	Percentage of patients (WHO grade) I	II	III	IV
Malaise	19	17	5	—
Dyspnea	17	15	—	—
Anorexia	17	8	—	—
Nausea/vomiting	10	7	—	—
Alopecia	8	17	—	—
Fever/flushes	24	—	—	—
Anemia	20	14	—	—
Thrombocytopenia	20	—	—	—
Hepatotoxicity	14	—	—	—

Of 62 patients treated with high-dose tamoxifen, 3 patients were lost to follow-up. The remaining 59 patients were evaluated for clinical toxicity.

DISCUSSION

In the present clinical investigation, we treated 62 patients with tamoxifen. Tamoxifen was administered at a high dose of 100 mg/m²/day. Among 59 patients evaluable for treatment response, only one short-lived PR was achieved. Therefore, the objective response rate of this therapy was calculated at 1.7% (95% CI, 0.04–9.09%). This is in the range reported for the occurrence of unexplained spontaneous regression of metastatic renal cell carcinoma [1].

These results were consistent with recent reports, demonstrating that hormonal therapy had at best a marginal effect against metastatic renal cell cancer [15], that responses were infrequent, incomplete and short-lived, and did not improve survival to any degree [16]. In a review of 110 patients, DeKernion *et al.* found no patient with an objective response upon endocrine therapy [17]. The actual existence of remissions induced by hormonal manipulations is highly controversial [5]. Hrushesky and Murphy noticed a decline in response rates of hormonal therapy, as stricter response criteria were applied to study populations [4]. Given recent WHO evaluation standards, response rates upon antioestrogen therapy do not surpass the rate of spontaneous remissions, as shown in this report.

Systemic side-effects were considerable, with two toxic deaths ascribed to pulmonary embolism, and with grade III malaise occurring in 5% of patients, and grade II anaemia, dyspnea, alopecia and malaise in almost 20% of patients. In previous clinical studies employing high-dose tamoxifen, serious complications such as cerebral vascular accidents were reported [18, 19]. It has to be noted that toxicity occurred in advanced cancer patients in the palliative setting, where toxicity was not balanced by therapeutic benefit. It has therefore been suggested that systemic tamoxifen administered in the absence of disease progression may significantly worsen the therapeutic index [19].

In summary, tamoxifen as single-agent therapy appeared to be ineffective in our study cohort. However, recent reports have suggested a potential synergy between tamoxifen and recombinant cytokines such as interferon-α [20] and interleukin-2 [21]. Based on the present data and published reports, single-agent tamoxifen is not to be employed as first-line therapy in patients with metastatic renal cell carcinoma [18].

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Dihydropyrimidine Dehydrogenase Activity in Cancer Patients

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Dihydropyrimidine dehydrogenase (DPD) is the major catabolic enzyme of pyrimidines and fluoropyrimidines. The clinical course of 2 patients with suspected DPD deficiency is described. Both patients had significantly delayed clearance of fluorouracil (5-FU), elevated plasma uracil concentrations, and subsequent lethal toxicity. The prevalence of DPD deficiency in the general population is unknown, but given the large number of cancer patients treated with 5-FU, it may be of great clinical significance. Lymphocytes have been previously shown to be a useful marker of systemic DPD activity. Because DPD activity has not been previously reported in a large population of cancer patients using 5-FU as the substrate, we determined DPD activity in lymphocytes from 66 patients with cancer. DPD activity was determined by a sensitive high performance liquid chromatography method. The mean DPD activity (S.D.) in 66 patients with head and neck cancer was 0.189 (0.071) nmol/min/mg protein with wide interpatient variability (range 0.058–0.357). DPD activity was not correlated to age ($r = -0.164$, $P = 0.188$). The mean DPD activity in men [0.192 (0.074)] was not significantly different from that in women [0.172 (0.057); t-test $P = 0.418$]. Likewise, there was no statistical difference in DPD activity in patients who had not received prior chemotherapy [0.195 (0.066)] to patients receiving one or more cycles of chemotherapy [0.186 (0.074); t-test $P = 0.638$].
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INTRODUCTION

FLUOROURACIL (5-FU) is one of the most widely used and active anticancer drugs in treating digestive, breast, and head and neck cancer. Recent advances in basic and clinical research have enhanced the therapeutic efficacy of 5-FU with synergistic drug combinations (cisplatin, interferon) and methods of biochemical modulation (folinic acid, dipyridamole) [1].

While much research has focused towards correlating the complex anabolism of 5-FU with cytotoxicity [2], relatively little research has concentrated on discerning the contribution of 5-FU catabolism to its cytotoxicity. The extent of catabolism of 5-FU influences the availability of 5-FU for anabolic conversion to cytotoxic nucleotides [3]. In addition, 5-FU systemic exposure (5-FU plasma area under the concentration–time