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CLINICAL TRIAL REPORT

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High-dose toremifene in advanced renal-cell carcinoma

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Abstract Toremifene (Fareston) – a novel antiestrogenic drug with a triphenylethylene structure – is effective in the treatment of postmenopausal breast cancer patients. It can be safely given even at high doses of up to 300 mg/day. The purpose of the present study was to investigate the effect and tolerability of high-dose toremifene in the treatment of patients with advanced renal-cell carcinoma (RCC). A total of 36 patients started treatment with toremifene at 300 mg/day, including 26 men and 10 women. Their mean age was 56 years (range 35–75 years). In all, 19 patients were nephrectomized. One patient was not evaluable for response because of insufficient treatment time. The response rate was 17%, including one complete response (CR, 3%) lasting for 121+ weeks and five partial responses (PRs, 14%) with a mean duration of 40+ weeks. Ten cases of no change (NC, 28%) had a mean duration of 24 weeks. There was no significant difference in the response rate when patients with lung metastases alone were compared with patients showing metastases of other sites with or without lung metastases. Total pain control was achieved in 45% of the patients who had pain at the beginning of the treatment, and partial control was attained in 20%. Ten patients (28%) developed adverse reactions, which led to discontinuation of the treatment in one case. Blood samples were taken from 16 patients on days 0, 1, 3, 7, 14, and 28 for drug analyses. The concentration of toremifene and its main metabolites measured in serum were about 1.5 times that detected after a conventional dose of 60 mg/day. It can be concluded that high-dose toremifene is an effective and safe palliative treatment in advanced RCC.

Key words Advanced renal-cell carcinoma · High-dose toremifene · Fareston

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Introduction

Cytotoxic agents are only marginally effective in the treatment of advanced renal-cell carcinoma (RCC). Combining different cytotoxic agents does not improve the results [27]. In a review of 72 cytotoxic chemotherapeutic agents used singly or in two-drug combinations, only 197 of 3502 patients (6%) obtained a complete or partial response [38]. Hormonal therapy results in temporary tumor regression in fewer than 10% of patients [23]. Cytokines may be slightly more effective than cytotoxic agents or hormones [30]. Nonetheless, the results of palliative treatment of metastatic RCC remain unsatisfactory. Spontaneous regressions of metastatic lesions following radical nephrectomy are very rare [7].

The rationale of using hormones in the treatment of RCC arises from two main findings: the induction of RCC in male Syrian hamsters by estrogens and the findings of variable amounts of hormone receptors in RCC tissue [6, 15]. Despite some early promising results, hormonal treatment with androgens, corticosteroids, and progestins have not been very successful [11, 15, 19, 24]. Higher response rates have been achieved using high doses of medroxyprogesterone acetate (MPA, 2 g/day) especially in nephrectomized patients with metastases only to the lungs, but this treatment has been accompanied by severe, sometimes even fatal complications – thrombocytopenia and thrombosis of the vessels of the remaining kidney [25]. The reappearance of interest in the hormonal treatment

of advanced RCC was caused by the influence of the concentration of steroid hormone receptors on the efficacy of MPA treatment [8], by the effect of antiestrogens on the tumor growth of certain cell lines in vitro [12, 29], and by the suppressant effect of tamoxifen on RCC in Syrian hamsters [18].

A review of the clinical data concerning the use of tamoxifen and, in some cases, of nafoxidine in advanced RCC during the last 15 years shows that the objective response rates obtained in different studies were 6–7% following conventional doses of 20–40 mg/day and 12–19% following high doses (100 mg/m^2 per day) [1, 34]. This has led to contradictory conclusions with regard to the effect of tamoxifen [30, 34, 36]. Toremifene is a new triphenylethylene antiestrogen. It is as effective as tamoxifen in the treatment of postmenopausal breast cancer but can be used at higher doses, and it is not a liver carcinogen in rats [13, 14, 28, 32, 37].

Patients and methods

A total of 36 patients (26 men and 10 women) with histologically confirmed locally advanced and metastatic progressive RCC were enrolled into the present study during the period ranging from April 1991 to April 1993. The baseline characteristics of the patients are presented in Table 1. All patients had measurable or evaluable disease and a performance status of 0–2 on the ECOG scale and had not received prior chemotherapy or hormonetherapy. If radiotherapy had been given, the patients concerned were enrolled into the study at two months after its discontinuation. The patients had to have adequate renal (serum creatinine < 120 mmol/l) and hepatic [bilirubin < 30 mmol/l and ASAT (SGOT) ≤ 0.48 mmol/l] function, and a thrombocyte count of $> 150 \times 10^9$/l. The ethics committee reviewed the protocol and all patients were required to give informed consent.

Toremifene 60-mg tablets were supplied by Orion Pharma (Turku, Finland). The dose, 300 mg/day, was divided into three parts: 120 mg in the morning, 60 mg in the afternoon, and 120 mg in the evening. The treatment was continued until disease progression but for at least 6 weeks. The first follow-up assessment was done at 6 weeks and then monthly. Responses and adverse events were defined according to WHO criteria for the solid tumors [20]. Regular opthalmologic examinations were not performed during the study.

Blood samples were taken from 16 patients (13 men and 3 women) to determine the serum levels of toremifene and its metabolites during repeated high-dose treatment with toremifene (300 mg/day). The samples were taken before toremifene treatment and at 1, 3, 7, 14, and 28 days. The blood samples (5 ml) were taken from the cubital vein in the morning. Serum was separated and stored at $-20\,^{\circ}$C. The analyses were done in the bioanalytical laboratory of Orion Pharma (Turku, Finland) by a high-performace liquid cromatography (HPLC) method [3].

Fisher's exact test (two-sided) was used to compare the response rates of patients with lung metastases alone with those of patients displaying metastases of other sites with or without lung metastases and the response rates of nephrectomized patients with those of patients whose primary tumor had not been removed.

Table 1 Characteristics of patients

Characteristics	Number
All patients	36
Sex:	
M	26
F	10
Age (years):	
Mean	56.0
Range	35–75
Previous nephrectomy	19
Relapsed after nephrectomy	3/19
Extent of disease:	
Locally advanced	2
Primary tumor + metastases	15
Metastatic, primary excised	19
Tumor size:	
Mean	109 cm^2
Range	30–294 cm^2
Sites of metastases:	
Lymph nodes	17 (47.2%)
Lung	6 (44.4%)
Bones	9 (25.0%)
Soft tissues	5 (13.9%)
Pleura	3 (8.3%)
Liver	2 (5.6%)
Thyroid gland	1 (2.8%)
The other kidney	1 (2.8%)
Subjective symptoms (pain):	
Severe	10
Moderate	7
Mild	3

Results

One patient was lost after 1 month of treatment and was thus not evaluable for response. The objective response rate (intent to treat) was 17% (Table 2). One patient obtained a complete response (CR, 3%) lasting for 121+ weeks. Five patients obtained a partial response (PR, 14%) lasting for 40+ weeks (mean), the range being 9–74 weeks. For ten patients with no change (NC, 28%) the mean duration of stabilization was 24 weeks, the range being 9–69 weeks.

No difference was found in the response rate between patients with lung metastases alone (1/5, or 20%) and those showing metastases of other sites with or without lung metastases (5/30, or 17%, $P = 0.81$). The response

Table 2 Treatment results obtained in 36 patients (*CR* Complete response, *PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable)

Response	Number (%)	Response duration (weeks)	
		Mean	Range
CR	1 (2.8)	121+	–
PR	5 (13.9)	39.8+	9–74
NC	10 (27.8)	23.7	9–69
CR + PR + NC	16 (44.4)	30.0	9–121+
PD	19 (52.8)	–	–
NE	1 (2.8)	–	–

rate was somewhat higher in previously nephrectomized patients (5/19, or 26%) than in those whose primary tumor had not been removed (1/17, or 6%); However, the difference was not statistically significant.

In all, 20 patients suffered from pain before the beginning of the treatment and had to use opioid analgesics. In nine patients (45%), total pain control was achieved, and four patients (20%) achieved partial pain control after 1–2 weeks of treatment. In 10 of these 13 patients (77%), pain relief was observed despite the tumor progression.

No adverse event was registered in 25 patients (69%). Only one patient had to discontinue treatment because of grade III reversible elevation of ASAT (SGOT)/ALAT (SGPT) levels after 3 months of treatment. The other adverse events were rare and comparable with those appearing after conventional doses of toremifene or tamoxifen (Table 3). No clinical change in the visual acuity of the patients was seen.

Table 3 Adverse events

Adverse event	Number (%)
Nausea, vomiting (grade II–III)	3 (8.3)
Abdominal pain	1 (2.8)
Weakness, tachycardia	1 (2.8)
Flashes, sweating, menstrual disorders	1 (2.8)
Insomnia	1 (2.8)
Skin allergy	1 (2.8)
Hypercalcemia	1 (2.8)
Serum bilirubin elevation (grade I)	1 (2.8)
ASAT/ALAT elevation (grade II–III)[a]	4 (11.1)
Serum creatinine elevation (grade I)	3 (8.3)
No adverse event	25 (69.4)

[a]One patient discontinued treatment because of grade III toxicity after 3 months

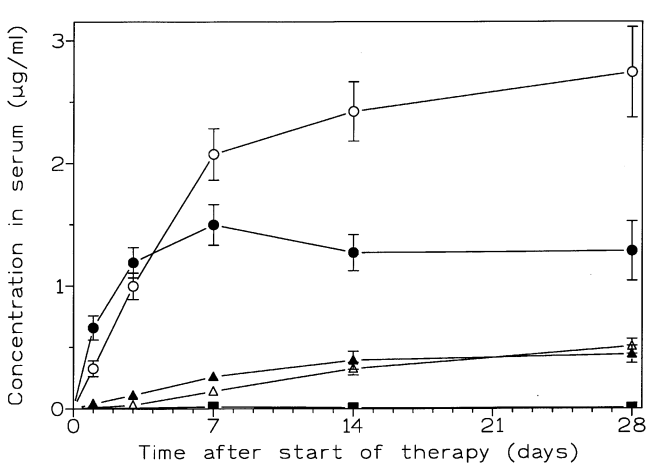

Fig. 1 Concentrations of toremifene and its metabolites measured in serum during repeated dosing of toremifene at 300 mg/day [● Toremifene, ○ *N*-demethyltoremifene, ▲ (deaminohydroxy) toremifene, △ *N*,*N*-didemethyltoremifene, ■ 4-hydroxytoremifene]

The concentrations of toremifene and its metabolites measured in serum are presented in Fig. 1. In 4 weeks, only toremifene reached the steady-state level (1.3 µg/ml). The concentration of the major metabolite, *N*-demethyltoremifene, was 2 times higher than that of toremifene at 4 weeks. At the same time the concentrations of two minor metabolites, (deaminohydroxy) toremifene and *N*,*N*-didemethyltoremifene, were less than half of that of toremifene. The fourth metabolite, 4-hydroxytoremifene, was barely detectable.

Discussion

The results of the present study are comparable with those obtained in previous studies with high doses of tamoxifen and better than those achieved with conventional doses of tamoxifen or with other hormone therapies [11, 15, 19, 23, 26]. It should be emphasized that the patients either had suffered a relapse or had progressive disease with bulky tumors. In case of lung metastases alone, toremifene was no more effective than tamoxifen at high doses [23, 30]. However, toremifene tended to be more effective (no statistically significant difference) in patients who had undergone nephrectomy. A similar phenomenon has been observed with biological response modifiers [22, 24, 26].

The considerable analgesic effect achieved in 1–2 weeks with toremifene at 300 mg/day has not been previously described and has not been seen following high doses of tamoxifen. This effect allowed a great number of patients with severe pain (45%) to avoid taking strong opioids. This analgesic effect did not coincide with the response to treatment but was seen in many patients with progressive disease.

The antiestrogenic side effects of toremifene are frequently hot flashes/sweating and, less often, vaginal symptoms such as bleeding and discharge. In addition to these non-dose-dependent effects, other, maybe incidental, effects were seen. Overall, the incidence of side effects tended to be low as compared with that seen in patients with breast cancer [12]. The dose-limiting toxicity of the drug typically involves nausea, vomiting, and disorientation [5]. Elevation of serum levels of liver enzymes due to the estrogenic action of the drug has also been described at higher doses [13]. The most frequent adverse events seen in the present study were nausea or vomiting and elevation of concentrations of liver transaminases, which most likely were due to the high dose used. Increased serum creatinine values were associated with the treated disease rather than with the drug. During recent years, immunotherapy with interferon-alpha and interleukin-2 alone or in combination with chemotherapy has been intensively studied in the treatment of RCC. However, the response rate has remained in the range of 10–20% for immunotherapy alone [21]. For the combination of immunotherapy

with cytotoxic drugs such as vinblastine, 5-fluorouracil, taxol, and anthracyclines, slightly better objective response rates have been seen [4, 9, 10, 15, 16, 17, 31–33]. However, the overall response rate achieved even in drug-combination trials, has been low and not substantially different from that obtained in single-drug trials, including the present study.

The concentrations of toremifene and its metabolites measured in serum in this study seemed to be 1.5 times those achieved with the conventional dose of 60 mg/day [2]. Though in two other studies the dose was not identical to that used in the present study, the steady-state concentrations achieved were similar to those obtained with high doses (200 and 400 mg/day and 200 mg/m^2 per day) [5, 35]. 4-Hydroxytoremifene, which was detected in small amounts, is not usually detectable following 60-mg/day dosing. In patients with advanced breast cancer the highest recommended dose was 300 mg/m^2 [5]. As the efficacy of toremifene in the treatment of RCC may be dose-dependent, a study to assess optimal dosing of the drug is warranted. We conclude that toremifene is a valuable drug in the palliative treatment of advanced RCC.

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