

Capecitabine in the treatment of metastatic renal cell carcinoma

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Summary To evaluate the therapeutic effects and systemic toxicities of a capecitabine-based home therapy regimen in patients with metastatic renal cell carcinoma, 30 patients were enrolled in a phase II clinical trial. Treatment consisted of oral capecitabine combined with subcutaneous recombinant human interferon- α 2a, recombinant human interleukin-2 and oral 13-cis-retinoic acid. There were two (7%) complete responses (CRs) and eight (27%) partial remissions (PRs), for an overall objective response rate of 34% (95% CI 17–53%). Except one, all responses are ongoing, with a median duration of 9+ and 8+ months for CRs and PRs, respectively. Additionally, 12 patients (40%) reached stable disease. Eight patients (27%) showed continued disease progression despite treatment. Therapy was well tolerated and was given in the outpatient setting. Capecitabine-related World Health Organization (WHO) grade 2 and 3 toxicities were observed in five and two patients respectively, and were limited to fatigue, nausea/vomiting, diarrhoea, stomatitis, dermatitis and hand-and-foot syndrome. The substitution of capecitabine for 5-FU in the pre-existing biochemotherapy regimen did not result in a reduced therapeutic efficacy and showed significant anti-tumour activity in patients with advanced renal cell carcinoma. © 2000 Cancer Research Campaign

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Renal cell carcinoma is known to be mostly chemotherapy-resistant (Hrusshesky and Murphy, 1977; Duensing et al, 1994; Yagoda et al, 1995). While the prognosis of patients with metastatic renal cell carcinoma remains poor, objective and durable remissions can be reached in approximately one third of patients using palliative biochemotherapies, especially employing combined cytokines and 5-fluorouracil (Lopez et al, 1996; Ellerhorst et al, 1997).

Capecitabine is an orally administered fluoropyrimidine carbamate, activated by a three-step conversion process to the cytotoxic agent 5-FU. After oral administration, capecitabine is first metabolized in the liver to 5'-DFCR. Second, 5'-DFCR is converted to 5'-DFUR by cytidine deaminase, located in high concentrations in the liver and tumour tissues (Takebayashi et al, 1996; Miwa et al, 1998). Finally, conversion of 5'-DFUR to 5-FU occurs by thymidine phosphorylase, which is present at higher concentrations in tumour than in normal tissue, thus minimizing the exposure of healthy body tissues to 5-FU (Takebayashi et al, 1996; Ishikawa et al, 1998a; 1998b). The efficacy and favourable safety profiles of capecitabine have been demonstrated in patients with common solid tumours such as colorectal and breast cancer (Blum et al, 1999; Mackean et al, 1998; Schüller et al, 1997). So far, no results have been reported in advanced renal carcinoma.

Here we report a phase II clinical trial of p.o. capecitabine combined with s.c. interferon- α 2a, s.c. interleukin-2 and p.o. 13-cis-retinoic acid. Systemic toxicity and therapeutic response were evaluated in 30 patients with progressive metastatic renal cell carcinoma. The results of this study are presented.

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PATIENTS AND METHODS

The study protocol was approved by the Clinical Institutional Ethical Review Board of the University of Hannover. Between June 1998 and December 1998 we entered 30 patients in a phase II clinical trial, (Table 1). All patients presented with histologically confirmed metastatic renal cell carcinoma in advanced state, aged 18–75 years, expected survival of more than 3 months, Karnofsky status of $\geq 70\%$, and signed informed consent.

Patients received the following capecitabine-based outpatient chemo-immunotherapy regimen. Interferon- α was administered subcutaneously at 5 MIU m⁻² on day 1 of weeks 5–8. Interleukin-2 was administered subcutaneously at 10 MIU m⁻² on days 3, 4 and 5 of weeks 1 and 4, and at 5 MIU m⁻² on days 1, 3 and 5 of weeks 2 and 3. Capecitabine was administered orally on days 1–5 of weeks 5–8 at 1000 mg m⁻² twice daily. In addition, oral 13-cis-retinoic acid was given at 34 mg m⁻² daily during weeks 1–8. Concomitant medication was given as needed to control adverse effects of immunotherapy. Patients were treated on an outpatient basis. Table 2 summarizes the therapy regimen used in this study.

8-week treatment cycles were repeated for up to three courses. Number of treatment cycles varied exclusively based on progressive disease of the patients. Re-evaluation of the patients' tumour status was performed between treatment cycles.

Response to therapy was evaluated according to World Health Organization (WHO) criteria: complete response = disappearance of all signs of disease for a minimum of 8 weeks; partial response = 50% or more reduction in sum of products of the greatest perpendicular diameters of measurable lesions, no increase in lesion size and no new lesions; stable disease = less than a partial response with no disease progression for at least 8 weeks; progressive disease = 25% and more increase in sum of the products in the

Table 1 Patients characteristics

Characteristics	Patients
Entered	30
Sex	
male	24
female	6
Age (years)	
median	60
range	38–73
Tumour nephrectomy	
yes	29
no	1
Metastases	
lung	23
bone	14
lymph nodes	12
liver	9
pleura	4
renal	4
adrenal gland	3
local relapse	1
other ^a	5
Prognosis ^b	
good	5
poor	25
No. of treatment cycles	46 (range 1–3)

^aTumour thrombus, soft tissue, pericardium, myelon ($n = 2$); ^bGood prognosis was defined by the presence of lung metastases and the absence of bone metastases, ESR < 70 mm after 1 h, serum lactic dehydrogenase < 280 units l⁻¹, neutrophilic granulocytes < 6000 μ l⁻¹ and haemoglobin > 100 gm l⁻¹ poor prognosis patients included all others

longest perpendicular diameters of measurable lesions, or development of new lesions.

Systemic toxicity was evaluated at weekly intervals using a grading system adapted from the World Health Organization (WHO).

Treatment efficacy was assessed on intent-to-treat basis.

RESULTS

Median follow-up and survival

Median follow-up of all patients is 8 months; except for three patients, all patients are still alive.

Treatment response

Out of 30 patients, two (7%) achieved a complete response, and eight (27%) had a partial remission (Table 3). The overall response rate in this study was 34% (95% CI 17–53%). Complete responses

(CRs) occurred in lung ($n = 1$), liver ($n = 1$), pleura ($n = 1$) and kidney ($n = 1$), while partial remissions (PRs) were seen in lung ($n = 4$), liver ($n = 3$) (Figure 1), bone ($n = 1$), pleura ($n = 1$) and local relapse ($n = 1$). The median response duration for CRs and PRs were 9+ and 8+ months, respectively, with a range from 4–10+ months (Table 4). Except for one patient who developed brain metastases, all patients are in sustained remission. In addition, 12 patients (40%) achieved stable disease upon chemotherapy (median duration of 8+ months). Eight patients (27%) had continued disease progression despite treatment.

Toxicity

In all patients, capecitabine therapy was completed without modification of dosage or change of time-interval. 25 of 30 patients reported capecitabine-associated, mostly mild side-effects (Table 5). No grade 4 toxicity was observed and only two patients reported grade 3 malaise, one of them with concomitant grade 3 nausea/vomiting and stomatitis. Grade 2 stomatitis, dermatitis, hand-and-foot syndrome, anorexia, diarrhoea and malaise were observed in four, two, two, two, one and one patients, respectively. Mild grade 1 gastrointestinal side-effects were reported in 16, and mild anorexia in nine patients with moderate dermatitis, five showed early stages of hand-and-foot syndrome in the upper extremity and/or nail disorders. Few patients ($n = 9$) developed grade 1 neurological symptoms including transient paraesthesia, headache and dizziness; eight patients reported mild myalgia. Grade 1 neutropenia was seen in one patient. No cardiac toxicity was noted; one patient with a history of severe aortic stenosis tolerated capecitabine without treatment-associated cardiac symptoms. In all patients treatment-related toxicities resolved after cessation of therapy. No toxic death occurred.

DISCUSSION

The use of biologic therapies has an established role in the treatment of metastatic renal cell carcinoma (Quesada, 1988; Belldgrun et al, 1991; Atzpodien et al, 1995a; Hofmockel et al, 1997). Potentially better results can be obtained using combination therapies with cytokines and 5-fluorouracil (Lopez et al, 1996; Hofmockel et al, 1997). Retinoids are known to control many important biological processes, including differentiation, morphogenesis, growth and tissue homeostasis (Warrel, 1994). Clinical and pre-clinical results provide evidence for an antiproliferative effect of 13-cis-retinoic acid in IFN- α -treated patients with renal cell carcinoma (Buer et al, 1995; Motzer et al, 1995). Furthermore, it seems to have a favourable effect in the treatment of renal

Table 2 Home therapy regimen

Therapeutic agent	Dose	Regimen
Recombinant interferon- α 2	5 Million IU m ⁻² s.c. 10 Million IU m ⁻² s.c.	Once daily, day 1, weeks 1 and 4; days 1,3,5, week 2 and 3 Once daily, days 1,3,5, weeks 5–8
Recombinant interleukin-2	10 Million IU m ⁻² s.c. 5 Million IU m ⁻² s.c.	Twice daily, days 3,4,5, weeks 1 and 4 Once daily, days 1,3,5, weeks 2 and 3
Capecitabine	1000 mg m ⁻² p.o.	Twice daily, days 1–5, weeks 5–8
13-cis-retinoic acid	35 mg m ⁻² p.o.	Daily, days 1–7, weeks 1–8

Patients were entered between June 1998 and December 1998. Patients received cytokines and chemotherapy at home. Treatment cycles were repeated every 2 months for an average of 1.5 cycles (range 1–3) unless disease progression occurred

Table 3 Response to therapy

Tumour site ^a	Response				
	Complete remission	Partial remission	Stable disease	Progressive disease	Total
Lung	1	6	10	6	23
Bone	1	3	7	3	14
Lymph nodes	–	2	4	6	12
Liver	–	4	2	3	9
Pleura	1	1	1	1	4
Kidney	1	–	1	2	4
Adrenal gland	–	–	2	1	3
Local relapse	–	1	–	–	1
Other	–	1 ^b	3 ^c	1 ^d	5
Patients	2	8	12	8	30
Risk ^e Good/Poor	1/1	2/6	2/10	0/8	5/25

^aPatients may have had more than one tumour site; ^bSoft tissue; ^ctumor thrombus, pericardium, myelon; ^dmyelon; ^eGood Prognosis was defined by the presence of lung metastases and the absence of bone metastases, ESR < 70 mm after 1 h, serum lactic dehydrogenase < 280 units l⁻¹ neutrophilic granulocytes < 6000 µl⁻¹ and haemoglobin > 100 gm l⁻¹, poor prognosis patients included all others

Table 4 Remissions

Age (years)	Sex	Interval between first diagnosis and appearance of metastases (months)	Sites of metastatic disease upon capecitabine, αINF, IL2, 13-cis-RA	Prognosis ^a upon start of therapy	Maximal response to capecitabine, αINF, IL2, 13-cis-RA	Remission duration (months) from start of capecitabine, αINF, IL2, 13-cis-RA	Status
64	m	11	Lung	Good	CR	9+	alive
71	f	14	Kidney, pleura, bone	Poor	CR	9+	alive
41	f	0	Lung, lymph nodes, liver, bone	Poor	PR	4 ^b	alive
50	m	0	Lung	Good	PR	9+	alive
57	m	10	Lung, liver, local relapse	Poor	PR	8+	alive
57	m	25	Bone, soft tissue	Poor	PR	10+	alive
58	m	8	Liver, lymph nodes	Poor	PR	7+	alive
58	m	19	Lung, liver, pleura	Good	PR	8+	alive
64	m	23	Lung	Poor	PR	5+	alive
69	m	12	Lung, bone	Poor	PR	8+	alive

^aGood prognosis was defined by the presence of lung metastases and the absence of bone metastases, ESR < 70 mm after 1 h, serum lactic dehydrogenase < 280 units l⁻¹ neutrophilic granulocytes < 6000 µ l⁻¹ and haemoglobin > 100 gm l⁻¹, poor prognosis patients included all others; ^bThis patient developed brain metastases

cancer, when added to immuno-chemotherapy regimens (Atzpodien et al, 1995b).

Capecitabine, as a novel fluoropyrimidine carbamate which is converted to 5-fluorouracil by three enzymes located in the liver and in tumours, shows promising response rates and remission durations while being very well tolerated in patients with metastatic renal cell carcinoma. Due to four-fold higher thymidine phosphorylase (5-DFUR to 5-FU) activity in tumour compared to adjacent healthy tissue (Frings, 1998), capecitabine allows for a more specific anti-tumour therapy than conventional i.v. fluorouracil.

In the present home-therapy trial, we treated 30 patients with progressive metastatic renal cell carcinoma with a combination of p.o. capecitabine, s.c. IFN-α, s.c. IL-2 and 13-cis-RA. The dose of capecitabine was adapted on an empirical basis from the recommend dose (Roche Laboratories Inc, 1998). The continued administration over an extended treatment interval of 4 weeks in combination with s.c. IFN-α, as opposed to an administration for 2 weeks followed by a 1-week rest period, required both a reduction in the daily dose of capecitabine and a > 50% reduction in cumulative 8-week capecitabine dosages. Capecitabine shows promising objective response rates in various solid tumours (Frings, 1998).

We report first clinical results of capecitabine in the treatment of advanced renal cancer.

Tumour regressions occurred in 34% of patients evaluated, with 7% CRs, and median response duration of 8+ months. These results were comparable to other 5-FU-based therapy regimens in renal cell carcinoma (Sella et al, 1994; Joffe et al, 1996; Hofmockel et al, 1997; Tourani et al, 1998).

In the patients reported here, the rate of capecitabine-related toxicity was low, and side-effects were moderate overall. Predominant side-effects included gastrointestinal toxicities with diarrhoea, nausea/vomiting, dyspepsia and stomatitis, and cutaneous symptoms including dermatitis and early stages of hand-and-foot syndrome. A few patients experienced mild malaise and mild neurological/musculoskeletal side-effects.

Capecitabine-associated systemic toxicities were mostly limited to WHO grade 1, rarely grade 2. Only two patients experienced WHO grade 3 effects. It should be noted that in addition to capecitabine all patients were simultaneously treated with s.c. IFN-α and p.o. 13-cis-RA.

This confirmed the excellent tolerability reported in other malignancies at various dosages and treatment intervals of

Table 5 Systemic toxicity of capecitabine^a

Side-effects ^b (WHO criteria)	No. of patients			
	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	16	4	1	—
Diarrhoea	6	1	—	—
Nausea	15	—	1	—
Vomiting	7	1	1	2–
Stomatitis	7	4	1	—
Abdominal pain	7	—	—	—
Constipation	6	—	—	—
Dyspepsia	9	—	—	—
Skin and subcutaneous	17	2	—	—
Hand-and-foot syndrome	5	2	—	—
Dermatitis	17	2	—	—
Nail disorder	4	—	—	—
General	14	1	2	—
Fatigue	14	1	2	—
Pyrexia	7	—	—	—
Neurological	9	—	—	—
Paraesthesia	1	—	—	—
Headache	5	—	—	—
Dizziness	6	—	—	—
Insomnia	—	—	—	—
Metabolism	9	2	—	—
Anorexia	9	2	—	—
Dehydration	2	—	—	—
Eye	1	—	—	—
Eye irritation	1	—	—	—
Musculoskeletal	8	—	—	—
Myalgia	8	—	—	—
Cardiac	—	—	—	—
Oedema	—	—	—	—
Blood	1	—	—	—
Neutropenia	1	—	—	—
Thrombocytopenia	—	—	—	—
Anemia	—	—	—	—
Lymphopenia	—	—	—	—
Hepatobiliary	—	—	—	—
Hyperbilirubinaemia	—	—	—	—

^aCapecitabine associated toxicities were evaluated during weeks 5–8 of each treatment cycle according to WHO criteria and were observed in 25 of 30 patients. Grade 2 toxicity was seen in five patients and grade 3 toxicity occurred in two patients; ^bPatients may have had several side-effects.

capecitabine (Budman et al, 1998; Mackean et al, 1998). Per oral administration of capecitabine, in contrast to most chemotherapeutic agents that are applied intravenously, allows treatment in an outpatient or home therapy setting. This advantage will reduce expenses and could enhance quality of life in the palliative setting.

Unless randomized data become available, the contribution of capecitabine and its potential therapeutic feasibility cannot be definitively assessed. Therefore, we have initiated a prospectively controlled randomized clinical trial to investigate the role of capecitabine in patients with advanced renal cell carcinoma.

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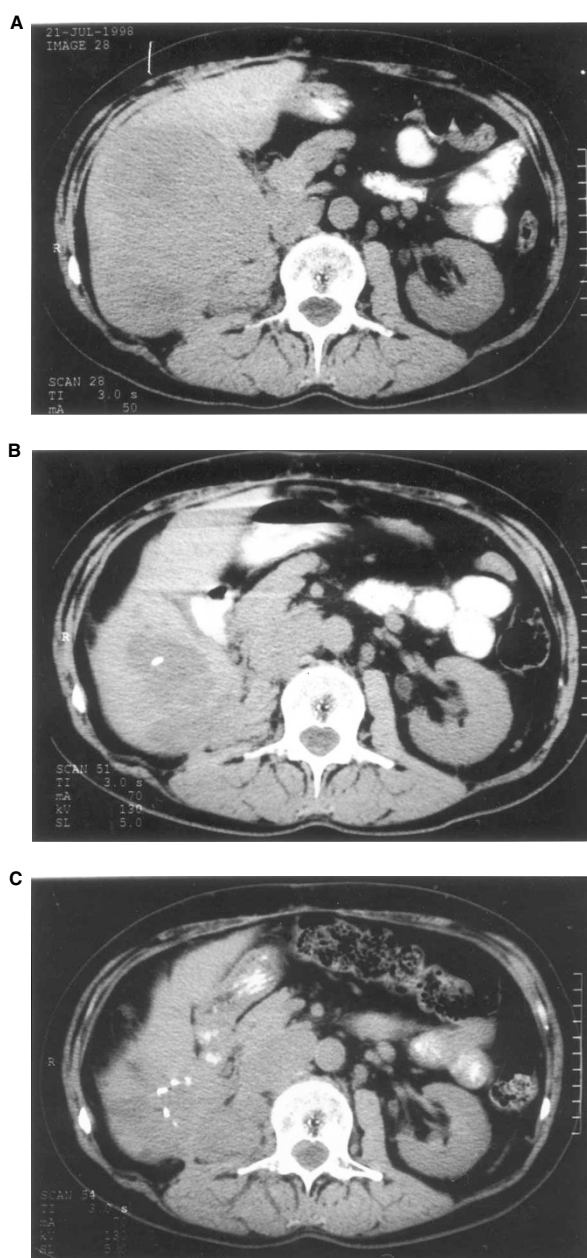


Figure 1 Liver CT scans of a 58-year-old patient with a history of advanced renal cell carcinoma, post-surgical of tumour nephrectomy and partial liver resection who (A) subsequently developed extensive metastatic lesions in his liver. (B) Partial remission of metastatic liver disease after the first 8-week treatment cycle with p.o. capecitabine, s.c. INF- α ; s.c. IL-2 and p.o. 13-cisRA. (C) Further tumour regression upon completion of the third consecutive treatment cycle.

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