Capecitabine as third-line treatment in patients with metastatic renal cell carcinoma after failing immunotherapy

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The aim of this study was to evaluate the activity and toxicity of capecitabine as third-line treatment in patients with advanced renal cell carcinoma for whom immunotherapy had failed. Twenty-one patients with metastatic clear renal cell carcinoma were enrolled. Capecitabine was administered orally twice daily at a dosage of 2500 mg/m^2 for 14 days, followed by 7 days of rest. The median number of administered cycles was five (1–13). One patient (4.8%) achieved a remission after eight treatment cycles. Stable disease was observed in nine patients (42.8%), whereas 11 progressed (52.4%). The estimated median time to progression was 3.6 months (confidence interval: 1.4 to 5.2). The estimated median overall survival was 7.2 months (confidence interval: 4.6 to 8.8). The regimen was well tolerated and no unexpected toxic effects were observed. Capecitabine as third-line treatment showed a favourable toxicity profile, but exhibited low activity in patients with advanced renal cell carcinoma after failing immunotherapy. ***Anti-Cancer Drugs*** **18:817–820 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Renal cell carcinoma (RCC) is unresponsive to conventional chemotherapy agents and therapy of metastatic disease remains inadequate [1]. The most used systemic therapy for metastatic RCC is immunotherapy, and cytokines such as interleukin (IL)-2 and/or interferon (IFN)-α usually achieve responses in 10–15% of patients, and occasional complete remissions may be observed; median survival is rarely superior to 12 months [2].

Significant advances in the treatment of clear-cell RCC have been recently derived from the oral multiple-kinase inhibitors sorafenib and sunitinib. Sorafenib exhibited interesting activity in phase II and phase III clinical trials, and achieved a statistically significant superiority in progression-free survival (PFS) compared with that for the controls in patients with advanced progressive RCC after one earlier systemic therapy [3,4].

Sunitinib achieved a 26–37% overall response rate in patients with cytokine-refractory metastatic RCC [3,5]. A randomized phase III study demonstrated a statistically significant improvement in PFS and objective response rate for sunitinib over IFN-α in first-line treatment of patients with metastatic RCC [6].

Chemotherapy may have a role in the treatment of a selected population of patients, e.g. exponential or rapidly growing clear-cell or uncommon renal pathology. The combination of doxorubicin and gemcitabine has shown antitumour activity in patients with sarcomatoid RCC or with rapidly progressing RCC [7]. Among the other chemotherapeutic agents, 5-fluorouracil (5-FU) has previously shown some activity, with partial remissions in about 10% of patients with metastatic RCC [8,9]. The combination of continuous infusion 5-FU with weekly gemcitabine showed an improvement in PFS over historical controls in patients with metastatic RCC [10].

Capecitabine is an orally administered prodrug of 5-FU, which has demonstrated considerable single-agent activity and a favourable safety profile in metastatic breast and colorectal cancer [11,12]. This drug is an oral thymidine phosphorylase (TP)-activated fluoropyrimidine, converted by a three-step conversion process to the cytotoxic agent 5-FU. The high tumour selectivity of capecitabine is achieved through exploitation of the significantly higher activity of TP in tumour tissue compared with that of healthy tissue [13]. Tumour types known to have a high level of TP activity, such as renal cancer, are possible targets for capecitabine therapy. A recent phase II study

reported a 20% response rate in patients with metastatic RCC treated with IFN-α, capecitabine and thalidomide [14].

The aim of this study was to evaluate the activity and toxicity of capecitabine as third-line treatment in patients with advanced RCC against which immunotherapy had failed.

Patients and methods

The eligibility criteria included patients with histological confirmation of metastatic or advanced unresectable clear RCC, bidimensionally measurable or evaluable disease, Eastern Cooperative Oncology Group performance status ≤ 2, of age 18 years or older, with no evidence of brain metastases, and adequate haematological (leukocytes $\geq 3000/mm^3$; haemoglobin ≥ 10 g/dl; platelets $\geq 100\,000/mm^3$), renal (serum creatinine ≤ 2.0 mg/dl) and hepatic (serum bilirubin ≤ 2.0 mg/dl) function. Patients were accepted only if they had progressed after first and second-line immunotherapy. Those who had undergone chemotherapy earlier were also admitted, with the exception of 5-FU and capecitabine. All of the patients gave their informed consent, and the protocol was approved by the Ethics Review Board of Siena University.

Treatment plan and assessment of response

Capecitabine was administered orally twice daily, within 30 min after a meal at a dose of 2500 mg/m^2 for 14 days, followed by 7 days of rest. All of the patients were treated on an outpatient basis. At study entry, all of the patients had their blood chemistry profiles, computed tomography scans of the chest–abdomen and brain, and a bone scan taken. Tumour measurements were performed after every three 21-day treatment cycle by computed tomography scan of the chest and abdomen, according to the Response Evaluation Criteria for Solid Tumors [15]. Bone scintigraphy was repeated every 6 months in patients who had also bone metastases. Response duration was measured from the first documented response to treatment to the first documented signs of disease progression. The time to progression (TTP) was the interval between the start of treatment and the date on which disease progression was first documented. Survival was measured from the date of the start of treatment to the date of death.

Toxicity

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria, version 2.0. Treatment was delayed if, on the planned day of treatment, the neutrophil count was $< 1500/mm^3$, the platelet count was $< 100\,000/mm^3$, or if the patient had persistent diarrhoea or stomatitis grade > 1. If grade 3 toxicity occurred, drug administration was withheld until the toxicity recovered to grade 1 or less and capecitabine was then reduced by 25–50% at the investigator's discretion. Capecitabine was permanently discontinued if grade 4 toxicity occurred.

Statistical considerations

According to Simon's minimax two-stage design, considering a 10% response rate as a level of interest for a third-line treatment in advanced RCC, at least 21 patients were required for an α and β error probability of 0.10 and 0.10, respectively. TTP and overall survival (OS) were estimated according to the method of Kaplan and Meier.

Results

Twenty-one patients with metastatic pure clear-cell RCC were enrolled between May 2002 and December 2005. Their median age was 61 years (range 46–77). Seventeen patients (80.9%) had lung metastases, 18 (85.7%) had received an earlier nephrectomy, and all of the patients had received first- and second-line immunotherapy. The performance status was 0–1 in 16 patients and 2 in five patients. Nineteen patients (90.5%) had more than one metastatic site (Table 1).

One patient received only one 21-day capecitabine treatment and then he was lost to follow-up: this patient

Table 1 Patient characteristics

Number of patients	21
Median age, years (range)	61 (46–77)
Sex	
Male	13
Female	8
ECOG PS	
0	3
1	13
2	5
Histology	
Clear-cell renal carcinoma	21
Prior nephrectomy	18
Prior first-line immunotherapy	
Subcutaneous low-dose IL-2	13
IFN-α	5
IL-2 + IFN-α	3
Prior second-line immunotherapy	
Subcutaneous low-dose IL-2	5
IFN-α	11
IFN-α + vinblastine	5
Prior radiotherapy	6
Involved sites of disease	
Lung	17
Liver	5
Bone	6
Lymph nodes	5
Renal	3
Pancreas	2
Pleura	1
Adrenal gland	1
Number of metastatic sites	
1	2
2	14
>2	5

ECOG PS, Eastern Cooperative Oncology Group performance status; IFN, interferon; IL, interleukin.

was considered as treatment failure according to intent-to-treat analysis.

The other patients received at least two 21-day treatment cycles: two patients were lost to follow-up after three treatment cycles. The median number of administered cycles was five (ranging from 1 to 13 cycles). One patient (4.8%) achieved a remission of more than 90% on liver, lung and adrenal metastases after eight treatment cycles: the response duration has presently reached 11 months. This patient had received prior left nephrectomy for renal cancer 4 months before entering the study; at the time of relapse, progression had been observed to first line IL-2, whereas stable disease (SD) had been obtained with second-line IFN-α.

Of the other patients, SD was observed in nine patients (42.8%), whereas in 11 patients (52.4%), the disease progressed. The estimated median TTP was 3.6 months (confidence interval: 1.4–5.2). The estimated median OS was 7.2 months (confidence interval: 4.6–8.8).

Toxicity

The regimen was well tolerated and no unexpected toxic effects were observed. No grade 4 toxicity was observed. The most frequent side effect was diarrhoea, which reached grade 1 or 2 in most cases. Grade 3 diarrhoea occurred in only one patient. Grade 3–4 stomatitis and/or hand–foot syndrome were not observed. Grade 3 neutropenia occurred in two patients and grade 3 anaemia in one patient. The capecitabine dose was reduced by 25% in three patients and by 50% in one patient.

Discussion

Immunotherapy with IL-2 and/or IFN-α is considered the standard treatment for advanced RCC, but response rates and OS are usually low [16]. Promising results in terms of improvement of objective response and PFS were reported with the multiple-kinase inhibitors sorafenib and sunitinib, and these oral agents were recently approved by the Food and Drug Administration for the treatment of metastatic RCC [3]. Despite new developments in the treatment of metastatic RCC, however, this disease cannot be cured with any known systemic therapy and it is generally considered to be relatively resistant to chemotherapy [17].

In this study, we treated 21 patients with metastatic pure clear-cell RCC, for whom first- and second-line immunotherapy had failed, with the oral fluoropyrimidine capecitabine. Tumour regression was observed in 4.8% of patients, SD in 42.8%. Despite a partial remission superior to 90% in one patient who had multiple metastatic sites (liver, lung and adrenal) and the response duration presently reached 11 months, the overall response rate was low in our population study. The overall median TTP was only 3.6 months, which resembles that seen with cytokines or therapy of limited activity in previously treated patients. The OS of 7.2 months was somewhat short. Therefore, these findings suggest a low activity of capecitabine treatment after immunotherapy with IL-2 and IFN-α failure in metastatic RCC.

Slightly better results have been reported in a few small studies that have evaluated capecitabine alone or in combination with immunotherapy in the treatment of advanced RCC. Wenzel *et al.* [18] reported a 9.6% partial response and 61.6% SD with capecitabine alone, but only 12 evaluable patients received the drug as third-line therapy.

Oevermann *et al.* [19] treated 30 patients with progressive metastatic RCC with a combination of capecitabine, IFN-α, IL-2 and 13-*cis*-retinoic acid. Although an interesting 34% response rate and 40% SD were observed, the real contribution of capecitabine could not be assessed owing to the use of a combination of several agents. The study by Padrik *et al.* [20] reported a 24% response rate, 36% SD and 4 months of PFS in 30 patients with advanced RCC treated with capecitabine and IFN-α: grade 3–4 toxicity occurred in 12 patients. Another study by Chang *et al.* [21] investigated the toxicity and maximum tolerated dose of capecitabine and IFN-α in 27 pretreated patients with advanced RCC: partial remission was documented in one patient, whereas grade 3–4 diarrhoea and neutropenia were observed. The recent study by Amato *et al.* [14] reported a 20% partial response, 4% minor response and 24% SD in 27 patients with metastatic RCC treated with IFN-α, capecitabine and thalidomide. This study suggested that capecitabine in combination may offer additional activity compared with the single-agent activity reported. Also, there appears to be a substantial number of patients who had SD for up to 3.5 months. Given the limited toxicity and activity reported with the delay in tumour growth with a single agent, there appears to be enough activity to move into combination.

Other studies investigated capecitabine combined with other chemotherapeutic drugs in the treatment of advanced RCC. A 15.8% response rate and 7.6 months TTP, with manageable toxicity, was reported in a phase II study of capecitabine and gemcitabine, in which the majority of the 21 enrolled patients had received only one earlier treatment regimen [22]. Another study described unacceptable toxicity in patients with advanced RCC treated with a fixed dose rate of gemcitabine combined with capecitabine [23]. Stadler *et al.* [24] recently reported that the modest activity of gemcitabine and capecitabine and its associated toxicity in patients with metastatic RCC would not support further evaluation in a phase III trial of unselected patients. Therefore, it seems

there is actually a lack of robust data supporting the use of capecitabine combined with other chemotherapeutic agents, whereas the combination of capecitabine with the novel molecular target agents such as sorafenib and sunitinib might be considered.

As expected, capecitabine was well tolerated, also in extensively pretreated patients. No grade 4 toxicity was observed and dose reduction by 50% was required in only one patient. Myelosuppression was also mild.

In conclusion, capecitabine as third-line treatment showed a favourable toxicity profile, but exhibited low activity in patients with metastatic RCC after failing immunotherapy.

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