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Short Communication

Phase I trial of metastatic renal cell carcinoma with oral capecitabine and thalidomide

Phase-I-Studie zum metastasierten Nierenzellkarzinom mit oralem Capecitabin und Thalidomid

Anja Kraemer[1]
Stefan Hauser[2]
Young Kim[1]
Marcus Gorschlüter[1]
Stefan C. Müller[2]
Peter Brossart[1]
Ingo G. H. Schmidt-Wolf[1]

1 Department of Internal Medicine III, University of Bonn, Bonn, Germany

2 Department of Urology, University of Bonn, Bonn, Germany

Abstract

Background: The highly vascular nature of renal carcinoma cells suggests that inhibition of angiogenesis may be beneficial in this disease. Thalidomide has been described as inhibitor of the fibroblast growth factor (FGF) and the vascular endothelial growth factor (VEGF). Therefore and in consideration of the promising response rates of the combination of IL-2, IFN-alpha and 5-FU [1] in metastatic renal cancer, we found it reasonable to test the combination of 5-FU and thalidomide. Thus, we conducted a phase I trial to determine safety, side effects and responses to such a treatment.
Methods: Patients with metastasized renal cell cancer after nephrectomy and progress after IL-2 and interferon treatment, received oral 5-FU at a dose of 1250 mg/qm^2 twice a day for two weeks, then after pausing a week, the oral application was restarted. In addition, oral thalidomide was applied constantly at a maximum dose of 400 mg/d. The combined therapy was given for three months. The primary endpoint was duration until disease progression, the secondary endpoint the response to treatment. Response was determined by CT scans three months after the end of treatment.
Results: In total, 12 male patients participated in the trial and received the combined oral therapy. Concerning clinical response, one mixed response (8%), a stable disease in 4/12 patients (33%) and progression was seen in 7 patients (58%). The survival from the start of the therapy showed a median of 21 months with three patients being alive. At present, the longest survival after the therapy is 51 months.
Conclusions: The combination of oral 5-FU and thalidomide showed clinical response with tolerable side effects. Further studies will be required to assess the outcome of this treatment regimen.

Keywords: metastasized renal cell carcinoma, 5-FU, thalidomide, phase I trial

Zusammenfassung

Hintergrund: Die hohe Vaskularisierung beim Nierenzellkarzinom legt nahe, dass eine Inhibition der Angiogenese bei dieser Erkrankung von Vorteil sein könnte. Thalidomid wurde als Inhibitor von FGF (Fibroblastenwachstumsfaktor) und VEGF (vaskulärer endothelialer Wachstumsfaktor) beschrieben. Deshalb und aufgrund der erfolgversprechenden Daten von Interleukin-2, Interferon-alpha und 5-FU [1] testeten wir die Kombination von Thalidomid und 5-FU. Wir führten eine Phase-I-Studie zur Testung von Sicherheit und Verträglichkeit durch.
Methoden: Patienten mit metastasiertem Nierenzellkarzinom nach Nephrektomie und Progress nach IL-2 und Interferon-Behandlung erhielten orales 5-FU in einer Dosierung von 1250 mg/qm^2 zweimal täglich über 2 Wochen. Nach einer einwöchigen Pause, wurde die Behandlung fortgesetzt. Zusätzlich wurde Thalidomid kontinuierlich bis zu einer maximalen Dosis von 400 mg/Tag gegeben. Diese Kombination erhiel-

ten die Patienten über 3 Monate. Primärer Endpunkt war die Dauer bis zur Progression der Krankheit, sekundärer Endpunkt das Ansprechen auf die Therapie. Das Ansprechen wurde mittels CT 3 Monate nach Ende der Therapie bestimmt.
Ergebnisse: 12 männliche Patienten nahmen an dieser Studie teil. Ein gemischtes Ansprechen (8%), 4 stabile Erkrankungen (33%) und 7 Progresse (58%) wurden gesehen. Das mittlere Überleben betrug 21 Monate mit jetzt noch 3 lebenden Patienten. Zur Zeit beträgt das längste Überleben 51 Monate.
Schlussfolgerung: Die Kombination von oralem 5-FU und Thalidomid zeigte bei diesen überwiegend vortherapierten Patienten klinisches Ansprechen bei tolerablen Nebenwirkungen. Weitere Studien sind notwendig, um den Stellenwert dieser Kombination nach Gabe der neuen Therapieoptionen beim metastasierten Nierenzellkarzinom zu untersuchen.

Introduction

The frequency of the renal cell carcinoma is increasing. A prevalence of 9/100.000 inhabitants in Germany and more than 30.000 new diagnoses in Europe underlines its enormous importance.
Renal cancer shows a peak of the disease at the ages between 50 and 70 years. A third of the patients with renal cell carcinoma present with metastases, mostly of the lung (60%), liver (25%) and skeleton system (25%).
A common therapy is yet to be established, while different strategies have been tested until now. The combination of IL-2 and IFN-alpha (plus 5-FU) showed a response rate of 37% [1].
Clear renal cell carcinoma is the major histological type. The tumor shows a high expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Therefore, we used thalidomide, which has antiangiogenetic and immunomodulatory properties, which showed a prolonged duration until disease progression in phase II studies in patients with metastasized renal cell carcinomas [2]. Showing neurotoxical side effects such as peripheral neuropathia neccesitating dose reductions after prolonged therapy with thalidomide alone, we decided to base our therapy on a combination with different chemotherapy [3].
Former studies described the use of 5-FU as a treatment for metastasized renal cell carcinoma in combination with IL-2 and IFN-alpha. This combination showed an overall response rate of 37%, while lowering the toxicity of an aggressive IL-2 treatment [1]. Being used in the treatment of colo-rectal carcinoma and breast cancer patients, it has also shown its efficacy in renal cell carcinoma (RCC) in several studies [4], [5].

Materials and methods

Patients

This phase I trial has been conducted between 2003 and 2006 and included 12 patients with metastasized renal cell carcinoma.

Criteriae for participating in the study has been histologically confirmed renal cell carcinoma at stage IVA, age 18 years or older, exclusive treatment in this study and an interval of lack of chemotherapy for at least two months. Patients signed written consent forms as approved by the local ethics committee.

Evaluation before, during and after treatment

The evaluation before treatment included a physical examination, a complete blood count, the Karnofsky index and a thorax and abdominal CT. The blood count was controlled every month in addition to liver function test and renal parameters such as creatinine. Posttreatment evaluations included the same parameters as the pretreatment evaluation.

Treatment and follow-up studies

Patients, who had filled in the main criteria for the study, had been given 1250 mg/qm^2 5-FU orally for two weeks, twice a day. Then after a pause for one week, the two-weekly cycle started again. Meanwhile the patients received constantly thalidomide at an individual dose, with an upper limit of 400 mg/d. Follow-up studies concentrated on a complete blood count, the subjective side effects of the therapy and post-treatment CT.

Assessment of efficacy

All patients where regularly evaluated for their subjective feeling of side effects. The response to the chemotherapy was evaluated after three months of treatment. The efficacy was jugded by the Response Evaluation Criteria in solid tumors (RECIST).

Statistical methods

Primary endpoint was the duration until disease progression, the secondary endpoint was response rate. In parallel, we concentrated on toxicity, which had been assigned by using the toxicity scale of the World Health Or-

Table 1: Patient characteristics

Characteristics	Distribution in participants (N=12)
Sex	
male	12
female	0
Age at diagnosis	
mean	58 years
range	35–78 years
Side of the primary tumor	
left	8
right	4
Nephrectomy	
yes	11
no	1
TNM-stage at diagnosis	
I	2
II	2
III	6
IV	
Metastases	
yes	12
no	0
Grading	
average	2
range of gradings	1–4
Duration until first metastases	
average	5.3 years (n=6)
range	0.25–14 years (n=6)
metastases at primary diagnosis	6
Pretreatment	
Systemic therapy[a]	
yes	8
no	4

[a] IL-2 and IFN-alpha

ganisation (WHO), the response rate was assessed by the RECIST criteria [6].

Results

Twelve patients participated in this phase I study and received the combined therapy. Table 1 summarizes the characteristics of the patients, their individual tumor stage, the grading and their systemic pretreatment. Median age was 58 years at the time of diagnosis. First, 11 of 12 patients had been nephrectomized, while 8 of them had received systemic treatment with IL-2 and IFN-alpha.

Response to treatment and duration until disease progression

The duration until disease progression had been evaluated by CT. The following criteriae had been used to define the results: CR: reduction to 0% tumor; PR: reduction to 1–50% tumor; MR: reduction 50–75% tumor, SD/NC: 75–125% tumor; PD>125% tumor.
The overall response showed a progression of metastases in 58% (7/12 patients), a stable disease in 33% (4/12) and a mixed response in 8% (1/12). Response seemed to show a correlation to the location of the metastases. The filiae in the lung seemed to be less responsive in comparison to the lymph nodule metastases, which showed a CR in one case. The duration until disease progression or regression was controlled individually between the first and third month after starting the therapy.
The kind of response after the first month correlated with the overall success or failure of the therapy. The patients who showed a lack of progression mostly stayed at a stable disease or showed a MR.
Those whose metastases increased in volume or numbers showed no response in the follow-up evaluations of the combined medication of thalidomide and 5-FU.

Toxicity

The most common side effects were gastrointestinal such as nausea, vomitting diarrhea or constipation (88%). Pain of the limbs were observed in 63%. Another side effect that seemed to be typical was the paresthetical feeling of the extremities (63%), especially the feet. Exanthemas were frequent (25%).

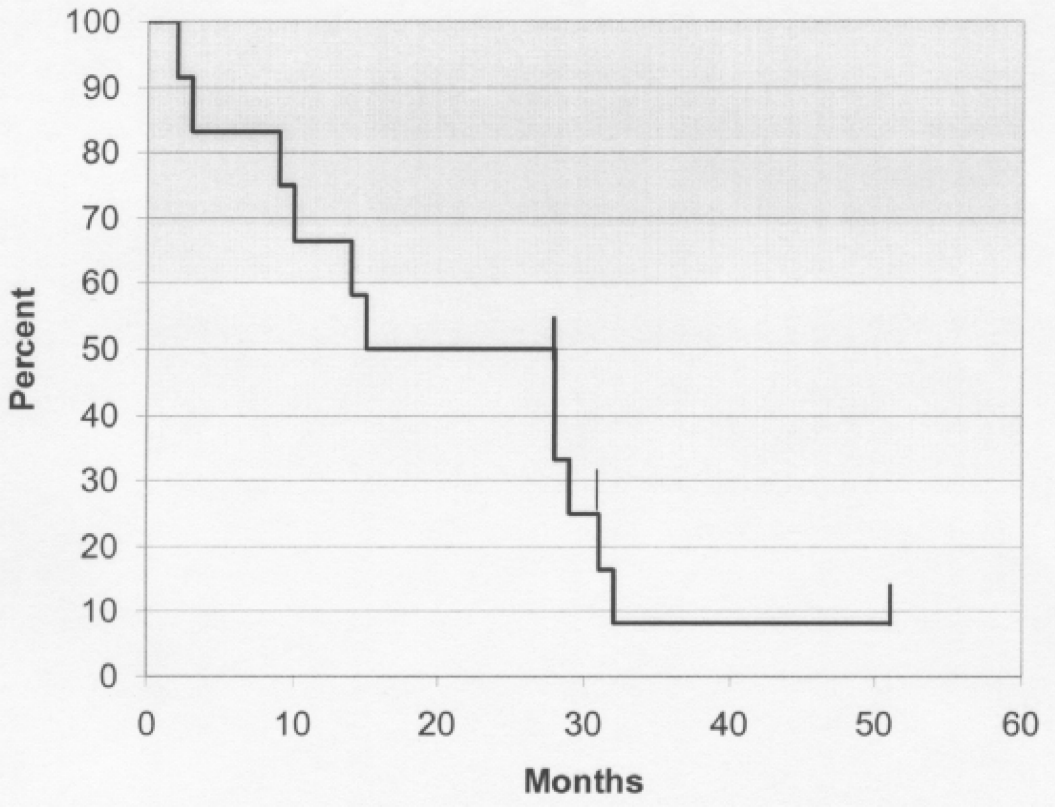

Figure 1: Overall survival of all 12 patients treated with oral 5FU plus thalidomide

The blood count showed no side effect. There was no liver or renal toxicity. Eleven patients received the complete dose of the chemotherapy except for one patient, who needed a dose reduction of 50%. One participant was excluded from the study because of unbearable paresthetical feelings.

Outcome and survival

At the end of the study, 75% (9/12 patients) had died of their disease. The longest survival showed a duration of 51 months (see Figure 1). Our study focused on the side effects the patients suffered under during the combinatory therapy. Those seemed to be tolerable.

In particular, the often described thrombosis under thalidomide therapy did not appear in this study, although thrombocytes raised during the treatment.

The raising of the thrombocytes was in none of the cases a reason for dose reduction or pausing of the therapy. The response to the therapy has to be established in further studies.

Discussion

In comparison to the studies of Hofmockel et al. [1], where IL-2, IFN-alpha and 5-FU had been given and the thalidomide/IL-2 therapy by Schrader et al. [7], the treatment of this phase I study consisted of thalidomide in combination with 5-FU.

While the treatment of Hofmockel et al. showed a promising response rate with 2 CR, 9 PR and an overall response rate of 37% with mild side effects, the therapy with thalidomide/IL-2 showed lower response rates and higher side effects.

Combining 5-FU with thalidomide allowed a dose reduction and therefore minor side effects during the treatment with thalidomide. With an overall response rate of 41.6% and minor side effects containing mostly constipation and paresthetical feelings of the limbs, just one of the participants discontinued treatment because of side effects.

With three patients, who survived since starting the study, the longest survival being 51 months, the outcome for the patients seemed to have improved for the patients who responded to the therapy in the first three months.

In their review, Hilles JJ and Kolesar JM reported of the use of sunitinib and sorafenib, both tyrosine kinase inhibitors with a potency in inhibiting the vascular endothelial growth factor (VEGF) receptors and the platelet-derived growth factor (PDGF) and therefore having an antitumor and antiangiogenic effect are also showing improved outcomes for patients with RCC [8]. Sunitinib is now used as treatment for metastatic renal cancer patients. In addition, sorafenib demonstrated to have a positive influence on the survival of patients with metastatic renal cell carcinoma in a phase III study [8].

As side effects of this therapy new studies described an induced macrocytosis under the treatment with sunitinib. This increase of the mean corpuscular volume (MCV) seemed to appear especially in patients with a diagnosed

hypothyreodism and were reversible after pausing the therapy. Cytopenia was reported with the use of both drugs [9]. Sunitinib induced hypothyreodism as a common side effect, which can be medically substituted with oral thyroide hormone replacement [10].

Another way of inhibiting the VEGF is the use of the humanised anti-VEGF monoclonal antibody bevacizumab. This has been combined with IFN-alpha. The results of this study showed a progression-free survival of 10.2 months [11]. In comparison to the application of IFN-alpha alone, the combination of both drugs showed a significant improvement in progression free survival [12]. The toxicity of IFN-alpha alone explains the necessity to search for a therapy with minor side effects while showing at least a similary response.

According to the EAU-Guidelines, the standard first and second line treatment for patients with metastasized renal cancer is tyrosin kinase inhibitors, since they increase progression-free survival. Hudes G. et al. showed in a comparison of temsirolimus, a specific inhibitor of the mammalian target of rapamycin kinase, to IFN-alpha alone, that temsirolimus treated patient improved in the overall survival by showing minor side effects. In particular, poor prognosis patients improved under the treatment, while a combination of temsirolimus with IFN-alpha had no significant effect at the overall survival in comparison to temsirolimus alone [13].

Our study is in accordance with a recent trial on the use of thalidomide plus interleukin-2 and GM-CSF in patients with metastatic renal cancer [14]. Comparing our study with the latest studies with our treatment our patients showed an overall survival up to 51 months, with tolerable side effects of the chemotherapy. The results seem to show that a response to the therapy can be seen in the first three months. Those who were responding to the therapy showed an improvement of their disease, while the side effects of the therapy were minor.

Notes

Conflicts of interest

None declared

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Corresponding author:
Prof. Dr. Ingo G. H. Schmidt-Wolf
Department of Internal Medicine III, University Hospital Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany,
Tel.: +49 228-287-15507, Fax: +49 228-287-15849
Ingo.Schmidt-Wolf@ukb.uni-bonn.de

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