Application of thalidomide/interleukin-2 in immunochemotherapy-refractory metastatic renal cell carcinoma

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Thalidomide has been reported to yield anti-tumor activity in advanced renal cell carcinoma (RCC). We evaluated safety and efficacy of a combination therapy comprising interleukin (IL)-2 and thalidomide in patients with metastatic RCC refractory to both immuno- and chemotherapy. Twelve patients with progressive metastatic RCC who had failed prior treatment with immunochemotherapy and desired further active therapy were enrolled in this study. Oral thalidomide was started at 200 mg/day and escalated after 2 days to 400 mg/day at week 0. IL-2 at 7 MIU/m^2 was given by s.c. injection, starting at week 1, days 1–5, weeks 1–4, with rest from IL-2 at weeks 5 and 6. Response was assessed every two therapy cycles. Ten patients were evaluable for response. There was no objective response; four patients showed stable disease for 14+, 11+, 10+ and 9 months, respectively. Toxicities were predominantly grade I–II, and included somnolence and constipation, as well as flu-like symptoms associated with IL-2. However, one patient developed serious constipation which led to a paralytic ileus and discontinuation of treatment. Another patient left the study after 7 weeks due to increasing disorientation/confusion. Eight patients required IL-2 dose reduction. Time on therapy ranged from 3 to 44 weeks (median 20 weeks). Median overall survival was 12+ months. At present, all patients have discontinued treatment. We conclude that outpatient administration of thalidomide/IL-2 is feasible in patients with heavily pretreated and progressive RCC who desire further active treatment. However, toxicity and costs are considerable, and clinical benefit is uncertain. Therefore, thalidomide/IL-2 might not represent a promising therapeutic approach for this subgroup of patients. *Anti-Cancer Drugs* **16:581–585**

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Introduction

Renal cell carcinoma (RCC) is a common urologic cancer and accounts for about 3% of all human malignancies. Estimates of annual new diagnoses of RCC have been increasing steadily [1]. Surgical resection of the primary tumor for patients with localized disease remains the mainstay of therapy. However, renal cancer is characterized by a lack of early warning signs, resulting in a high proportion of patients with metastases at diagnosis. Moreover, even after radical nephrectomy, 20–30% of all patients with primarily localized disease will eventually relapse [2]. The outlook for patients with distant metastases is poor, with a 5-year survival rate of less than 10% [1]. Metastatic RCC has proven to be resistant to chemotherapy as well as radiotherapy [3]. Immunotherapy with interleukin (IL)-2 or interferon (IFN)-α achieves response rates in 10–20% of patients with metastatic RCC [1,2,4–6]; combination therapies of IFN-α and IL-2 with or without chemotherapy show response rates up to 20–35%. Most responses occur in patients with pulmonary or soft tissue metastases [1,3,7,8]. However, responses achieved are predominantly partial remissions of short duration [1,2]. There is no standard treatment for patients who relapse following primary immunotherapy, resulting in a multitude of experimental second- and third-line therapeutic regimens being published over the last decade. The most promising approaches applied regimens based on 5-fluorouracil (5-FU) [9], capecitabine [10], retinoic acid [11], toremifene [12], vinorelbine/IFN-α [13], IL-2/IFN-α/5-FU [14] and vinblastine/IFN-α [15,16]. However, most salvage treatment strategies achieved disease stabilization of short duration only.

Thalidomide is an immunomodulatory agent that blocks angiogenesis [17], inhibits cytokines (tumor necrosis factor-α, basic fibroblast growth factor and vascular endothelial growth factor) [17,18] and modifies cell adhesion molecule expression [19]. Based on this activity, thalidomide has successfully been applied in the

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treatment of various malignancies including multiple myeloma and Waldenstrom's macroglobulinemia [20], glioma [21], Kaposi's sarcoma [22], and malignant melanoma [23], as well as erythema nodosum leprosum. Recently, several studies indicated activity of thalidomide-based regimens also in metastatic RCC with response rates ranging from 0 to 22% and disease stabilization in 13–64% of patients [19,24]. Nevertheless, several authors reported considerable thalidomide-related, dose-dependent toxicity, especially somnolence, constipation, lethargy, venous thromboembolism and, increasing with prolonged therapy, neurotoxicity [18,19,25–27].

The aim of this study was to evaluate the safety and efficacy of a combination therapy combining biological response modifiers and thalidomide in a homogenous group of patients with metastatic RCC refractory to first- and second-line immunochemotherapy.

Methods

Between July 2003 and January 2005, 12 patients were treated in this pilot clinical trial at the Philipps University Marburg Medical School and the University of Cologne, in accordance with the Declaration of Helsinki. Written informed consent with regard to the realization of the study protocol and the treatment-associated side-effects was obtained from all patients. All patients were required to have histologically confirmed RCC with evidence of progressive, bidimensionally measurable metastatic disease, adequate organ function and a life expectancy of 3 months or more. At least 4 weeks had to have elapsed since the last treatment. Patients were excluded if they had history of other malignancies except basalioma within the previous 5 years or CNS metastases. Patients of child-bearing age were eligible provided that they were practicing adequate contraception and all patients were fully informed about the teratogenicity of the drugs.

Oral thalidomide was started at 200 mg/day and escalated after 2 days to 400 mg/day at week 0. IL-2 at 7 MIU/m^2 was administered by s.c. injection, starting at week 1, days 1–5, weeks 1–4, with rest from IL-2 at weeks 5 and 6. Thalidomide was supplied in 100 mg capsules (Durbin, South Harrow, UK), and was administered orally at night. IL-2 (Chiron, Munich, Germany) was given at night flanked by oral acetaminophen 500–1000 mg. In patients who developed persistent grade II–III IL-2-associated toxicity the dose was reduced to 50%; in case of allergic reactions or intolerable toxicity, IL-2 was switched to IFN-α (Roche, Grenzach, Germany), at 9 MIU (s.c., once a day) 3 times a week during weeks 1–4, with a rest on weeks 5 and 6.

Evaluation of treatment-associated toxicity was performed every other day during the first 2 weeks and every 4 weeks thereafter. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Moreover, patients were followed monthly by a standardized questionnaire, physical evaluation, complete blood count and chemical survey.

Patients were considered evaluable for response if they had received therapy for at least 3 months (i.e. two cycles) and if they had undergone complete restaging of disease including computed tomography scans after every other cycle. Complete response (CR) was defined as the disappearance of all clinical and radiographic evidence of tumor persisting for at least 4 weeks. Partial response (PR) was defined as a 50% or greater decrease in the sum of the products of diameters of all measurable lesions persisting for at least 4 weeks without the development of any new lesions. All other responses were defined as stable disease (SD). Progressive disease (PD) was defined as a 25% or greater increase on the sum of the products of diameters of all measurable lesions or the appearance of any new lesion. Overall survival (OS) was defined as the time from the start of thalidomide treatment to death. Treatment was stopped in case of PD or intolerable toxicity.

Results

All 12 patients entered into this study were suffering from advanced refractory progressive metastatic RCC and had a significant disease burden. They exhibited a poor performance status (ECOG 1–3). The median age was 65 years (range 40–74 years). All patients had undergone radical tumor nephrectomy. The majority ($n = 11$, 92%) had presented with three or more metastatic sites, and seven patients (58%) had previously received two or more types of medical treatment including biological response modifiers (IL-2, IFN-α) and chemotherapy (5-FU, vinblastine). Patient characteristics are summarized in Table 1.

Two patients were not evaluable for response. Both stopped treatment before the end of the second cycle due to intolerable toxicity (Table 1). The first patient (no. 11), a 68-year-old female, presented with considerable disorientation and confusion after 4 weeks of treatment which increased steadily. Therapy was discontinued after the first cycle. The second patient (no. 12) suffered from unmanageable constipation which led to a serious paralytic ileus after 3 weeks of treatment. He had never experienced bowel disorders before.

Among the remaining 10 evaluable patients, no objective responses were observed, but disease was stable in four patients (33%). The first patient (no. 1; Table 1) had presented with metastases in the lung and mediastinum, his ECOG performance status was 2. He had progressed with IL-2, IFN-α and 5-FU as well as IFN-α and

Table 1 Patient characteristics

Patient	Age/sex/ ECOG	Metastatic sites	Previous treatment (cycles)	Thalidomide-based treatment (cycles)	Outcome (months)	Toxicity (CTC grade)
1	69/M/2	lung, mediastinum	SRM, IL-2/IFN-α/5-FU (3), vinblastine/IFN-α (4)	standard dosage (2), IL-2 50% reduced (3)	SD (14+)	constipation (2), fatigue (2), FLS, fever (3)
2	60/M/1	lung, mediastinum, retroperitoneal, thyroid gland	IL-2/IFN-α/5-FU (4), vinblastine/ IFN-α (4), IL-2/IFN-α (3)	standard dosage (5), IL-2 50% reduced (1)	SD (9)	constipation (2), fatigue (1), skin (1), nausea (1), dyspnea (2–3)
3	72/F/2	lung, mediastinum, RP, pancreas	IFN-α/vinblastine (3), IL-2/IFN-α/ 5-FU (2)	standard dosage (2), IL-2 50% reduced (4)	SD (10+)	constipation (2), fatigue (2), FLS
4	69/M/2	lung, mediastinum, RP	IFN-α/vinblastine (2), IL-2/IFN-α/ 5-FU (3)	standard dosage (2), IL-2 50% reduced (5)	SD (11+)	constipation (2), fatigue (2), FLS
5	63/M/2	lung, mediastinum, RP, bone	IL-2/IFN-α/5-FU (3), radiotherapy, temozolomide	standard dosage (1), IL-2 50% reduced (2)	PD	fatigue (2), FLS
6	40/F/3	lung, liver, RP, peritoneum	IL-2/IFN-α (4), IL-2/IFN-α/5-FU (3)	standard dosage (1), IL-2 50% reduced (2)	PD	constipation (3), FLS
7	62/M/2	LN, lung, mediastinum	IL-2/IFN-α/5-FU (4)	standard dosage (2)	PD	constipation (2), desquamation (1), FLS
8	74/M/3	LN, lung, mediastinum	IL-2/IFN-α/5-FU (2)	standard dosage (1), IL-2 50% reduced (1)	PD	constipation (2), fatigue (2), FLS, weight loss (3)
9	68/M/2	lung, liver, LN, bone	radiotherapy, IL-2/IFN-α/5-FU (2)	standard dosage (1), IFN-α instead of IL-2 (2)	PD	capillary leakage (3), constipation (2), fatigue (1),
10	58/M/2	LN, lung, pleura, mediastinum	IL-2/IFN-α/5-FU (4), pleurodesis (mitoxantrone)	standard dosage (2), IFN-α instead of IL-2 (1)	PD	dyspnea (3), constipation (2), fatigue (2), FLS
11[a]	68/F/3	RP, mediastinum, pancreas	IL-2/IFN-α/5-FU (3), SRM (2)	standard dosage (1)	(PD)	constipation (2), fatigue (3), FLS, disorientation/confusion (3)
12[a]	61/M/2	lung, mediastinum, pleura, bone, soft tissue	IL-2/IFN-α (3), IL-2/IFN-α/ vinblastine (4), gemcitabine/ peg-intron (3)	standard dosage	(PD)	constipation (4), fatigue (2), fluid retention (1), FLS

[a]Not evaluable for response.
ECOG = Eastern Cooperative Oncology Group, LN = lymph node, RP = retroperitoneum, SRM = surgical resection of metastases, FLS = flu-like symptoms, CTC = common toxicity criteria (ECOG).

vinblastine. He noted improved performance status after an IL-2 dose reduction due to flu-like symptoms and fever refractory to supportive treatment. However, he discontinued treatment after five cycles for personal reasons but, up to now, still remains in SD. The second patient (no. 2) had been treated with combination regimes including IL-2/IFN-α/5-FU, IFN-α/vinblastine and IL-2/IFN-α. However, he had failed to respond to any treatment. He was enrolled in the present study showing evidence of PD in the lung, mediastinum, retroperitoneum and thyroid gland. His condition improved considerably under treatment; he recovered appetite and gained weight. Toxicity was moderate with grade II constipation, and grade I fatigue and nausea. However, during the fifth cycle he complained about increasing dyspnea, which was successfully alleviated by IL-2 dose reduction. Unfortunately, he suffered a sudden massive disease progression after 9 months on treatment. The third patient (no. 3) had presented with lymph node and visceral metastases following five cycles of immunochemotherapy (IFN-α/vinblastine, IL-2/ IFN-α/5-FU). The fourth patient (no. 4) had also suffered from PD after five cycles of combined immunochemotherapy, and presented with pulmonary and lymph node metastases. They received a total of six and seven cycles IL-2/thalidomide therapy, respectively, resulting in an ongoing SD at all metastatic sites. Even though treatment-associated side-effects were moderate with constipation, fatigue and flu-like symptoms, in the latter two patients (no. 3 and 4) the IL-2 dose had to be reduced and treatment finally stopped due to significant interference with their daily life.

In summary, four patients achieved disease stabilization for 14+, 11+, 10+ and 9 months. At present, however, all patients have discontinued treatment. The remaining patients suffered PD (Table 1).

Short-term toxicity, e.g. somnolence and constipation, was observed in almost all patients (Table 1). Except for patient no. 12, constipation responded well to laxatives. Somnolence and lethargy were predominantly moderate, and even appreciated by a subset of patients by improving their sleep. Lethargy was most prominent at the beginning of therapy. Seven patients experienced grade III or greater toxicity. IL-2 was reduced to 50% in seven patients; two additional patients were switched to IFN-α to replace IL-2 (Table 1). Limiting toxicities leading to IL-2 reduction included grade III capillary leakage, dyspnea, fever and weight loss.

During the time of treatment no patient suffered clinically significant hematotoxicity, peripheral sensory neuropathy or venous thromboembolism. Time on therapy ranged from 3 to 44 weeks (median 20 weeks).

The median survival from the start of thalidomide-based treatment for all patients was 12+ months (range 5–16+ months). No patient died on treatment. Currently, eight patients are still alive.

Discussion

The paucity of effective therapeutic options for patients with metastatic RCC progressive following immunochemotherapy mandates investigation of new drugs and/or drug combinations. Single-agent thalidomide has been evaluated in several phase II studies (predominantly first-line), producing PRs in a median of 6% (range 0–22%) and SD in a median of 31% of patients (range 13–64%) [19,24]. Hernberg *et al.* were the first to apply first-line thalidomide/IFN-α combination to treat patients with metastatic RCC [24]. Twenty-seven patients were evaluable for therapeutic efficacy and a PR rate of 22% was reported. Another 17 patients (63%) had SD for at least 3 months and median survival time was 15.5 months. In 2004, Clark *et al.* [28] presented a similar phase II trial combining IFN-α and thalidomide as first-line therapy in 30 patients with metastatic RCC. In this study, only two patients had a PR (7%) and eight patients had SD (27%); the median survival time was 15.7 months.

A first study of low-dose s.c. IL-2 in combination with thalidomide (400 mg/day) was presented by Amato *et al.* at the 2003 ASCO Meeting [29]. In this phase II study of 37 patients who had received no previous chemotherapy or immunotherapy, there were 15 responders and 11 patients who achieved SD. The treatment was well tolerated with no reported grade 3 or 4 adverse events. Time on treatment ranged from 3 to 15 months. Kedar *et al.* [30] were the first to use an IL-2/thalidomide combination for patients who were refractory to first-line systemic treatment. They retreated four patients with advanced metastatic RCC who had experienced disease progression on IL-2 with the same IL-2-based regimen combined with oral thalidomide (300 mg/day). Two patients achieved PRs and prolonged disease stabilization (22 + and 18 + months).

Based these encouraging results, we hypothesized that the addition of thalidomide to IL-2 might result in improved response rates also in a significant fraction of patients with PD refractory to prior immuno(chemo)therapy. Twelve patients with metastatic RCC were treated with a combined IL-2/thalidomide regimen. All patients had advanced disease and poor performance status, associated with disease progression following primary local and systemic therapy and several salvage regimens. However, all patients desired further active treatment hoping to achieve disease stabilization and to maintain acceptable quality of life throughout the remaining period. Among 10 patients who were evaluable for response, no objective response was observed, but disease stabilization was achieved in four patients (33%) for 9–14 months. Three patients still remain progression free; however, all patients discontinued treatment due to a substantial reduction of their quality of life. The median survival from the start of thalidomide-based treatment for all patients was 12 months. Thus, the results of this pilot clinical study are in accordance with those of earlier single-agent thalidomide trials in patients with poor prognosis RCC. However, we could not reproduce the encouraging results by Kedar *et al.* [30] suggesting that the combined application of IL-2 and thalidomide could considerably improve response rates in heavily pretreated patients.

Since the current clinical trial was initiated in patients with end-stage metastatic RCC to maintain quality of life despite widespread metastases, treatment-associated toxicities were of major importance. In the literature, the most frequently reported thalidomide-caused toxicities are somnolence, lethargy and constipation; the most critical are neuropathy, thrombosis and venous thromboembolism [31]. The majority of side-effects appear to be dose and time dependent. Eisen *et al.* treated 18 RCC patients with a single dose of 100 mg thalidomide at night which was well tolerated without the development of grade III or IV toxicity [32]. In contrast, Escudier *et al.* administered oral thalidomide in an escalating regime up to 1200 mg/day. Treatment-associated toxicity was high, with frequent manifestations of grade III or higher fatigue (26%), lethargy (16%) and constipation (10%). The incidence of neuropathy assessed by clinical examination attained 70% at 6 months and 100% in patients on thalidomide for 12 months. Nine patients (23%) developed venous thromboembolism during the first 12 weeks of treatment and three of them experienced pulmonary embolism [25]. Similar results were rendered by Daliani *et al.* [33]. Moreover, toxicity appears to increase with combination therapies. Nathan *et al.* reported unexpected serious adverse events in 39% of patients treated with oral thalidomide (400 mg, daily) plus IFN-α (9 MIU, 3 times per week) [26]. At 31%, neurologic complications (including visual disturbance, seizures, loss of speech and numbness) were the most frequent and severe side-effects observed in this study. The authors suggested caution in combining these agents as both have membrane-destabilizing properties which might explain the excessive toxicity. Desai *et al.* used a combination of gemcitabine (600 mg/m^2, weekly), 5-FU (150 mg/m^2, daily) and thalidomide (400 mg, daily) to treat 21 patients with metastatic RCC [27]. They observed a high rate of venous thromboembolism; five patients (24%) developed deep vein thrombosis, three patients (14%) developed pulmonary embolization and one patient suffered a fatal cardiac arrest preceded by hemoptysis, for an overall venous thromboembolism rate of 43%. The authors recommended against the use of this combination regimen as the addition of thalidomide seemed to significantly increase vascular toxicity.

We used a regimen comprising intermediate-dose IL-2 and oral thalidomide to treat heavily pretreated patients with refractory metastatic RCC. Moderate to considerable somnolence, lethargy and constipation were

observed in almost all patients. One patient even developed a paralytic ileus and had to discontinue treatment after 3 weeks. Another patient received only one cycle of therapy suffering from progressive disorientation and confusion. Moreover, IL-2 was reduced to 50% in seven and discontinued in two patients due to severe toxicity including capillary leakage, dyspnea and intolerable flu-like symptoms. Only six out of 12 patients (50%) received at least two cycles of full-dose treatment. On the other hand, applying 400 mg of thalidomide combined with a cytokine for a maximum duration of 44 weeks, in our study no patient suffered clinically significant treatment associated peripheral sensory neuropathy, venous thrombembolism or hematotoxicity. However, the addition of IL-2 to thalidomide considerably increased toxicity; treatment was discontinued even in all responding patients predominantly due to IL-2-related side-effects.

Conclusion

Second- and third-line treatment of patients with metastatic RCC progressing under therapy with biological response modifiers and chemotherapy remains an unresolved issue. In the absence of access to alternative therapeutic options such as randomized clinical trials, thalidomide-based treatment can be considered for patients with desire for further active treatment. Nevertheless, toxicity is considerable and increasing with dosage. The addition of a cytokine such as IL-2 does not result in clinical benefit in a significant fraction of patients refractory to prior immunochemotherapy.

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