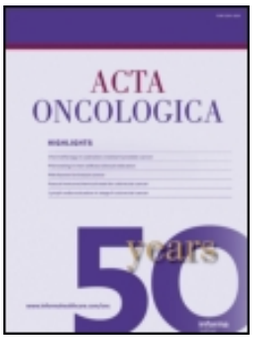

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ORIGINAL ARTICLE

Safety and efficacy of temsirolimus in heavily pretreated patients with metastatic renal cell carcinoma

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Abstract

Background. First line treatment with temsirolimus is considered standard of care in poor risk patients with metastatic renal cell carcinoma. The role of temsirolimus in pretreated patients with any risk profile is unclear. The aim of this retrospective analysis was to investigate the impact of temsirolimus in patients who had progressed on various treatment lines. *Material and methods.* From April 2007 to July 2009, all patients who had progressed on receptor-tyrosine kinase-inhibitors, VEGF-antibodies and other agents were treated with temsirolimus (25 mg weekly). Physical examination, white blood cell count and chemistry were obtained weekly and tumor response was assessed every 12 weeks. *Results.* Thirty patients with a median age of 68 years range (44–81) received treatment with temsirolimus. Most patients were categorized intermediate risk (60%) and the majority had three or more metastatic sites (56.7%). Temsirolimus was median the fourth (range 2–5) systemic treatment line. Grade 3 and 4 toxicities were rare and consisted of anemia, thrombocytopenia and hyperglycemia. Objective remission and stable disease were achieved in 13.3% and 60% of the patients, respectively. The median progression free survival was 4.9 months (2.93–6.81 95% CI). *Conclusion.* Temsirolimus appears feasible, safe and active in heavily pretreated patients.

Based on a better understanding of the biology of renal cell carcinoma (RCC), the therapeutic options for patients with metastatic RCC have substantially improved. Novel agents which inhibit the vascular endothelial growth factor (VEGF)-mediated angiogenesis have been approved in the last four years. The VEGFR-tyrosine kinase inhibitor sunitinib and the monoclonal anti-VEGF antibody bevacizumab in combination with interferon-alpha are considered the new standard of care in RCC patients with favorable or intermediate risk profile [1–3]. Both strategies were shown to confer statistically significant benefits in terms of objective response rates (ORR) and progression free survival when compared to IFN-alpha.

Only a small number of poor risk patients were included in these pivotal trials. Thus, it is less clear as to whether this patient population derives meaningful benefits from agents that inhibit VEGFR tyrosine kinases or VEGF itself. VEGF or VGEFR-tyrosine kinases may not necessarily represent the most crucial targets in poor risk patients. A retrospective analysis of patients treated with the mammalian target of rapamycin (mTOR)-inhibitor temsirolimus suggested that particularly patients with poor risk features may benefit from agents that target mTOR [4]. The serine/threonine kinase mTOR regulates cell growth and proliferation and was found to be important in the pathobiology of RCC [5], particularly in patients with aggressive tumor behavior [6]. To clarify as to whether mTOR-inhibition is clinically relevant in poor risk patients, a randomized phase III first-line-trial comparing temsirolimus, interferon-alpha and the combination of both agents was initiated in a specifically defined poor risk patient population. In this trial, patients treated with temsirolimus

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showed a 49% increase in median survival (10.9 vs. 7.3 months, $p = 0.008$) when compared to patients on interferon-alpha [7]. Moreover, temsirolimus was shown to have a favorable safety profile, with hypercholesterolemia and hyperglycemia being the most commonly reported adverse events. Accordingly, temsirolimus has been approved for the first-line treatment of patients with metastatic RCC and poor risk features.

The success achieved with this plethora of new first-line agents has rapidly brought attention to the topic of appropriate second-or third-line therapy in the case of disease progression. Several therapeutic strategies were investigated for their impact on the course of the disease after failure of targeted agents. Treatment with sorafenib in sunitinib-refractory patients was shown to enable a PFS of seven months, whereas sunitinib-refractory patients achieved a PFS of 4.25 months with sorafenib [8]. Similarly, up to 17% of sorafenib-refractory patients achieved ORR with subsequent sunitinib therapy [9,10]. Finally, when compared to placebo, second-line treatment with the oral mTOR-inhibitor everolimus was shown to provide a statistically significant benefit in terms of PFS (4 and 1.9 months, respectively, $p < 0.0001$, HR 0.30) in patients who had progressed on one or two VEGF-tyrosine kinase inhibitors [11]. Based on the results of this randomized phase III trial, everolimus is considered standard of care in this patient population.

Although everolimus and temsirolimus inhibit the same target and share similar pharmacodynamic properties, the role of temsirolimus in pretreated patients is unclear. A randomized trial is currently underway to investigate the use of temsirolimus after sunitinib failure but the study is not expected to be completed before May 2011 [12]. So far, even data from smaller pretreated patient series are lacking because access to temsirolimus has been restricted in many countries to first-line poor risk patients. Elsewhere, temsirolimus might be available for any treatment-line and for any risk group, allowing the entire RCC-patient population to have eventually access to this agent during their course of the disease. The same is true for the sequential use of receptor-tyrosine kinase inhibitors: sunitinib and sorafenib are often restricted to treatment-naïve and cytokine-refractory patients, respectively. This reduces both the total number of available treatment lines for the patients and the generation of data on sequencing of these drugs in a real world population. The aim of this retrospective analysis was to investigate the safety and efficacy of temsirolimus in heavily pretreated patients, i.e. patients who had progressed under various types of therapies.

Material and methods

Patients

Eligibility criteria included histologically confirmed metastatic RCC, a Karnofsky performance status of at least 60 and progression on prior VEGFR-tyrosine kinase inhibitors. Patients had to have measurable disease (according to the response evaluation criteria in solid tumors (RECIST criteria) [13]. Adequate renal, hepatic and bone marrow function were required and defined as a hemoglobin of at least 8 mg/dl, platelets of at least 100 000/m^3, neutrophils of at least 1500/m^3, serum creatinine of no more than 1.5 times the upper limit of normal and AST of no more than five times the upper limit of normal. Patients with brain metastases were treated for systemic disease after local treatment for brain metastases and were considered eligible if neurologically unsuspicious. Laboratory parameters including complete blood cell count and serum chemistry were performed at baseline and then weekly. Staging investigations were performed every 12 weeks and consisted of computed tomographic scans or magnetic resonance imaging if required. Response was evaluated according to RECIST.

Treatment

Treatment consisted of temsirolimus given weekly at a dose of 25 mg over 30 minutes. Premedication consisted of diphenhydramine given intravenously 30 minutes before the start of temsirolimus. Treatment was continued until disease progression or serious deterioration. No dose reductions were planned. For grade 2 adverse events that were poorly tolerated, treatment interruption was permitted at the discretion of the treating physician. In the case of grade 3 or 4 adverse events, treatment was withheld until recovery.

Statistical analysis

Statistical analysis was performed using SPSS for windows software (RE SPSS 14.0; SPSS, Chicago, IL, USA). Descriptive statistics of relevant demographic and clinical features were compiled. Survival time was evaluated using Kaplan-Meier survival curves.

Results

Between April 2007 and July 2009, a total of 30 patients (male $n = 21$, female $n = 9$) who had progressed under targeted agents were treated with temsirolimus at a dose of 25 mg.

Baseline characteristics

Baseline characteristics are outlined in Table I. The median age of the total patient population was 68 years (range 44–81 years). All patients had a Karnofsky Performance Status (KPS) of more than 70 and the majority (60%) was categorized as intermediate risk according to the Memorial Sloan Kettering Cancer risk group criteria (MSKCC) [14]. All patients had undergone nephrectomy. The most common metastatic site was the lung (90%), followed by bone (46.7%) and lymph nodes (46.7%). Most of the patients (56.7%) had three or more metastatic sites. Temsirolimus was median the fourth (range 2–5) systemic treatment line offered to the patients since diagnosis of metastatic disease. The most common previous therapies were sunitinib (86.7%), cytokines (70%), sorafenib (60%) and bevacizumab (33.3%).

Table I. Baseline characteristics.

Characteristics	median (range, %) n = 30
Age (median/range)	68 (44–81)
Sex	
Male	21 (70%)
Female	9 (30%)
Karnofsky Performance Score	
>70	30 (100%)
<70	0
Previous nephrectomy	30 (100%)
Histology	
Clear cell	28 (93.3%)
Non-clear cell	2 (6.7%)
Papillary	n = 1
Chromophobe	n = 1
MSKCC risk group	
Favorable	9 (30%)
Intermediate	18 (60%)
Poor	3 (10%)
Number of metastatic locations	
1	4 (13.3%)
2	9 (30%)
3 or 3+	17 (56.7%)
Metastatic locations	3 (1–5)
Lung	27 (90%)
Bone	14 (46.7%)
Lymph nodes	14 (46.7%)
Liver	8 (26.7%)
Pancreas	3 (10%)
Central nervous system	3 (10%)
Adrenal gland	3 (10%)
Other	5 (16.7%)
Line in which temsirolimus is used	
median/range	4 (2–5)
First	0
Second	5 (16.7%)
Third	6 (20%)
Fourth	11 (36.7%)
Fifth	8 (26.7%)
Systemic pretreatment	
Sunitinib	26 (86.7%)
Cytokine based	21 (70%)
Sorafenib	18 (60%)
Bevacizumab	10 (33.3%)
Gemcitabine	3 (10%)
Other	6 (20%)

Values expressed as number, (percentage), or median (range).

Tumor response, progression free survival (PFS) and overall survival (OS)

As outlined in Table II, four of 30 evaluable patients (13.3%) achieved objective remission (ORR), another 18 (60%) achieved stable disease for a clinical benefit rate of 73.3%. Responses were observed in patients with clear cell RCC only. The median PFS was 4.9 months (2.93–6.81 95% CI). The median OS for all patients was 14.2 months (13.69–21.45 9% CI). Patients with three prior anti-VEGF-therapies had a better chance for remission and a longer PFS when compared to those with one or two pretreatments. However, these differences were not statistically significant which is most likely related to the small number of patients in this analysis: ORR in patients with one, two or three prior anti-VEGF-treatment: 0%, 16.7% and 33.3%, respectively, $p = 0.13$; PFS in patients with one, two or three prior anti-VEGF-treatment: 4.9 (95% CI 2.4–7.3) months, 3.7 (95% CI 2.2–5.1) months and 7.5 (95% CI 2.7–12.3) months, respectively, $p = 0.61$.

Adverse events

The most common adverse events are outlined in Table III. The most common all grade toxicities were anemia (93.4%), thrombocytopenia (50%), hypercholesterolemia (43.3%), dyspnoea (43.3%), cough (40%), increase in AST (33.3%) and hypertriclyceridemia (33.3%). Grade 3 or 4 adverse events were rare and consisted of anemia (6.7%), thrombocytopenia (3.3%) and hyperglycemia (3.3%).

Table II. Outcome temsirolimus.

	All patients median n = 30	%
Best response		
CR	0	0
PR	4	13.3
SD	18	60.0
PD	8	26.7
	All patients median n = 30	**95% CI**
Progression free survival (median months)	4.9	2.93–6.81
Overall survival (median months)	14.2	13.69–21.45

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table III. Toxicity.

Adverse Event	Grade 1 + 2	Grade 3 + 4	All Grades
Asthenia	36.6%	–	36.6%
Rash	30%	–	30%
Anemia	86.7%	6.7%	93.4%
Thrombocytopenia	46.7%	3.3%	50%
Neutropenia	16.7%	3.3%	20%
Lymphopenia	33.3%	–	33.3%
Nausea	10%	–	10%
Anorexia	3.3%	–	3.3%
Vomitus	13.3%	–	13.3%
Diarrhea	16.6%	–	16.6%
Constipation	6.6%	–	6.6%
Weight Loss	26.7%	–	26.7%
Stomatitis	26.6%	–	26.6%
Abdominal pain	3.3%	–	3.3%
Increased Aspartate aminotransferase	33.3%	–	33.3%
Dyspnea	43.3%	–	43.3%
Cough	40%	–	40%
Hypertriclyceridemia	33.3%	–	33.3%
Hypercholesterolemia	43.3%	–	43.3%
Infection	13.4%	–	13.4%
Hyperglycemia	20%	3.3%	23.3%
Fever	3.3%	–	3.3%
Headache	3.3%	–	3.3%
Increased creatinine level	13.3%	–	13.3%
Peripheral edema	20%	–	20%
Erythema	13.3%	–	13.3%

Treatment delays and dose reductions (Table IV)

A total of 13 patients (43.3%) had treatment-associated dose delays for a median duration of 2.0 weeks (1.0–2.9 95% CI). One patient had a dose delay of 13.4 weeks which was due to a zoledronic acid-associated osteonecrosis of the jaw requiring surgery. The most common reasons for treatment delays were patient request (n = 5) and grade 2 thrombocytopenia (n = 5). One patient discontinued treatment due to grade 4 hyperglycemia. No patient had dose reductions.

Table IV. Reasons for dose delays and treatment discontinuation.

	n = 30	100%
Dose reductions	0	0%
Dose delays	14	46.6%
Dose delays treatment-associated	**13**	**43.3%**
Thrombocytopenia	5	16.6%
Hyperglycemia	1	3.3%
Patient request	5	16.6%
Increased creatinine level	1	3.3%
Infection	1	3.3%
Dose delays not treatment-associated (surgery)	1	3.3%
Treatment discontinuation	22	73.3
PD	20	66.6%
AE (grade 4 hyperglycemia)	1	3.3%
Patient request (schedule)	1	3.3%

PD, progressive disease; AE, adverse events.

Discussion

First line treatment with the mTOR inhibitor temsirolimus was shown to improve progression free survival and overall survival in patients with metastatic RCC and poor risk profile [7]. The aim of this retrospective analysis was to investigate the impact of temsirolimus in patients with any risk profile who had progressed under various types of therapies. The principal finding is that temsirolimus is safe and feasible in a pretreated patient population. Moreover, temsirolimus enabled a clinical benefit rate of 73.3% (ORR: 13%, SD: 60%) which was associated with a median PFS of 4.9 months and a median overall survival of 14 months. Slightly poorer results were observed in a recently published retrospective analysis on temsirolimus in pretreated patients. MacKenzie et al. reported on a PFS and OS of 3.9 months and 11.2 months, respectively [15]. The longer PFS in our patients might be biased by the 12 weeks- instead of eight weeks response-assessment. Differences in OS can be explained by the fact that 36% of the patients in the MacKenzie trial were MSKCC poor risk and 11.5% had not undergone prior nephrectomy. In contrast, the vast majority of our patients were good or intermediate risk (90%) and all were nephrectomized. Moreover, the 12 weeks response assessment in stead of the eight weeks assessment in the MacKenzie trial may account for the PFS difference.

The oral mTOR-inhibitor everolimus, which is currently considered standard of care in patients who had failed prior anti-VEGF-agents, was shown to enable objective remissions in 3 (1%) of 272 patients only [11]. With this data in mind, the number of patients showing partial remission in our small and heavily pretreated population appears quite encouraging. Two reasons may account for this difference. First, the favorable outcome of our population might in a sense be based on a selection bias. Although our patients were certainly burdened with the amount of prior therapies and treatment-related side effects, they also represent a positive selection, i.e. a population that survives long enough to be treated with median 3 prior lines. Second, in the phase III everolimus trial, the study drug had to be discontinued in 10% of the patients due to adverse events including pneumonitis, dyspnea and fatigue, another 34% and 5% of the patients required treatment interruptions for an unreported period and dose reductions, respectively. Consequently, an inappropriate dose density and dose intensity might have impaired the outcome in terms of objective remission. Although dose delays were also frequent (46.6%) in our patients, treatment could mostly be resumed very

early, i.e. after a median delay of 2.0 weeks and no patient had dose reductions.

The high rate of dose delays in our population is attributable to several factors: first, the patient's compliance was probably lower after several treatment lines: five of 30 patients (16.6%) requested a dose delay for non-toxic reasons, mainly due to the weekly administration schedule. Second, in another five patients, the dose was delayed due to thrombocytopenia (mostly grade 2), which was certainly an overestimated safety concern. This estimation is supported by an analysis of Gerullis et al. [16] who reported on a complete absence of both grade 3/4 toxicities and therapy interruption/dose reduction in patients who were treated with temsirolimus after sunitinib. Thus, the tight administration schedules of temsirolimus rather than the severity of adverse events may limit the use of temsirolimus after failure of anti-VEGF agents.

The role of second-line temsirolimus in sunitinib-refractory patients is currently under investigation in a phase III trial that compares temsirolimus with sorafenib [12]. Even if the results of this trial lead to approval of temsirolimus after TKI-failure it is questionable as to whether physicians would prefer intravenous temsirolimus with tight administration schedules over oral everolimus. A potential safety advantage of weekly temsirolimus over everolimus must be pronounced enough to pave the way for temsirolimus as an equally accepted second- or third-line agent. We rather believe that the favorable safety profile of temsirolimus should trigger focused research on combinations. Strong synergistic activity has recently been shown with the histone deacetylase inhibitor vorinostat in vitro [17]. In vivo, the combination of bevacizumab and temsirolimus has demonstrated interesting preliminary results in a phase I trial [18]. However, in a randomized phase II trial, this combination failed to demonstrate a clinically relevant synergistic/additive efficacy [19]. Finally, classical cancer treatment might be a valuable combination partner for Temsirolimus: in contrast to other tumors, mTOR-inhibitors exert their anti-tumor function in RCC predominantly by inhibition of angiogenesis [20,21]. To induce apoptosis as shown for endometrial cancer, higher concentrations of temsirolimus, which are barely reached in vivo, are required [20,21]. However, experimental studies suggest that the combination with strong inhibitors of apoptosis such as 5-fluorouracil or gemcitabine may also inhibit tumor cell proliferation in RCC.

In summary, our data support the use of temsirolimus in later treatment lines for patients with metastatic RCC and any risk profile. The safety of temsirolimus even in heavily pretreated patients should trigger investigations in combination with other agents.

Declaration of interest: Manuela Schmidinger has acted as an adviser to Pfizer, Novartis, Roche and GSK, has received research and travel grants from Pfizer and lecture fees from Pfizer, Novartis and Roche. Christoph Zielinski has acted as an adviser to Pfizer and Roche, has received lecture fees from Pfizer, Merck, Lilly and Roche. Gero Kramer has received research grants from Sanofi Aventis, Bayer-Schering and Takeda, lecture fees from Sanofi Aventis, Astra Zeneca and Astellas, acted as an advisor to Sanofi Aventis and received travel grants from Pfizer, Boehringer-Ingelheim, Sanofi Aventis and Bayer-Schering. Ursula Vogl, Wolfgang Lamm, Marija Bojic and Christoph Klingler have no conflicts of interest to declare. The authors alone are responsible for the content and writing of the paper.

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