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Phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma

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Summary

Sunitinib is associated with a robust objective response rate in patients with metastatic clear cell renal cell carcinoma (RCC). The primary objective of this phase II clinical trial was to assess the overall response rate for sunitinib in patients with papillary metastatic RCC as well as other non-clear cell histologies. A Simon 2-stage design was used to determine the number of papillary metastatic RCC patients for enrollment, and allowed for descriptive response data for other non-clear cell histologies. Twenty-three patients were enrolled, including 8 with papillary renal cell carcinoma (RCC) and the remainder with other non-clear cell histologies (unclassified in 5 patients). All patients received 50 mg of oral sunitinib in cycles of 4 weeks followed by 2 weeks of rest (4/2). The trial was stopped early because of slow accrual; no responses were observed in the 8 patients with papillary RCC. In the 22 evaluable patients, best response to sunitinib included a partial response in 1 patient with unclassified RCC, stable disease in 15, and progression in 6. The median progression-free survival was 5.5 months (95% CI, 2.5–7.1) in all 23 patients, and 5.6 months for the 8 papillary patients (95% CI, 1.4–7.1). The robust objective responses sunitinib had produced in clear cell RCC could not be demonstrated in this study comprised of patients with non-clear cell histologies.

Keywords

Papillary renal cell carcinoma; Non-clear cell renal cell carcinoma; Sunitinib; Phase II trial

Renal cell carcinoma (RCC) is composed of several histologies including clear (conventional), papillary, chromophobe, collecting duct/medullary, and unclassified cell types [1–6]. Clear cell, the predominant cell type, comprises approximately 80% of renal epithelial tumors. The remaining renal neoplasms, collectively identified as non-clear cell RCC, consist of papillary (the most common), chromophobe, collecting duct/medullary, and unclassified cell types [2]. Recently, an improved understanding of the mechanisms involved in RCC growth and angiogenesis has prompted the development and implementation of anti-angiogenesis targeted therapies in the treatment paradigm for metastatic RCC (MRCC). Small-molecule targeted inhibitors including sunitinib have demonstrated antitumor activity in randomized phase III clinical trials [7–13], and have assumed a predominant role in standard management for metastatic clear-cell RCC.

Historically, the non-clear cell histologies are characterized by poor prognosis and resistance to systemic chemotherapy and cytokine therapy in the metastatic setting [14–17]. Data on the efficacy of targeted therapy for non-clear cell subtypes is limited to a few retrospective studies [18], and overall remains poorly defined. We sought to evaluate the efficacy of sunitinib in patients with metastatic papillary RCC as well as other less common types of non-clear cell RCC.

Patient and methods

Patient eligibility

Twenty-three patients with metastatic papillary and other non-clear cell histologies were entered into a phase II clinical trial of sunitinib at Memorial Sloan-Kettering Cancer Center (MSKCC) from March 2007 to October 2009. Eligibility criteria included histologically

confirmed advanced RCC of papillary or other non-clear cell histology; evidence of measurable metastatic disease; Karnofsky performance status (KPS) $\geq 70\%$; absolute neutrophil count (ANC) $\geq 1,500$ cells/ μL ; platelet count $\geq 100,000$ cells/ μL ; hemoglobin ≥ 9.0 g/dL; serum calcium ≤ 12.0 mg/dL; serum creatinine ≤ 1.5 times the upper limit of normal; total serum bilirubin ≤ 1.5 times the upper limit of normal; serum AST and ALT ≤ 2.5 times the upper limit if liver function abnormalities were caused by underlying malignancy. Patients with tumors containing sarcomatoid features were eligible and there was no limit to the percentage of sarcomatoid involvement. Patients were excluded if they had received prior therapy with sunitinib or had major surgery or radiation therapy within 4 weeks of starting the study treatment. Before beginning treatment with sunitinib, each patient was evaluated with a history and physical examination, KPS determination, complete blood count, screening blood chemistry panel with electrolytes, thyroid panel, amylase, lipase, urinalysis, electrocardiogram, and appropriate radiographic imaging for measurable disease. A negative pregnancy test was required for women of childbearing potential. All patients gave informed consent; the trial was reviewed and approved by the Institutional Review Board at MSKCC. All pathology was reviewed and classified at MSKCC (VR and ST).

Treatment plan

Once daily, 50 mg of sunitinib was administered orally for 4 consecutive weeks followed by a 2-week break (4/2 schedule), comprising a complete cycle of 6 weeks.

Toxicity and response criteria

All toxicities were evaluated based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE, v3.0). Dose reductions were performed depending on the type and severity of toxicity encountered, as previously described [7]. Grade 4 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 fatigue, and grade 4 hand-foot syndrome resulted in a reduction of 1 dose level. In addition, patients were instructed to withhold sunitinib for grade 3 hand-foot syndrome and any other nonhematologic grade 3 or 4 toxicity until the toxicity reached grade ≤ 1 , with reinstitution at either the same dose level or 1 dose level reduction at the discretion of the investigator.

Interim assessment of tumor status was performed by radiographic imaging at baseline, every 6 weeks for cycles 2–4, then on even-numbered cycles (ie, 6, 8). Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST). Treatment was continued until disease progression ($\geq 20\%$ increase in tumor size), unacceptable toxicity, or patient withdrawal.

Statistics

The sample size and stopping rules were determined according to a Simon 2-stage design, in which a response rate of $\geq 20\%$ was considered promising and a response rate of $\leq 5\%$ was unacceptable [19]. With a type I error of 5% and a type II error of 20%, 12 papillary RCC patients would initially be enrolled and treated with sunitinib, with planned enrollment expanded to 37 patients with papillary RCC if at least 1 patient responded. The trial allowed for descriptive response data for other rare non-clear cell histologies. Slow accrual of patients with papillary histology caused early closure of the study.

Results

Patient characteristics

Twenty three patients began treatment with sunitinib (Table 1). The median age of study patients was 55; 18 (78%) patients had undergone prior nephrectomy. There was a relatively

high proportion of patients with lung (43%) and lymph node (83%) metastases. Sixteen patients (70%) had ≥ 2 metastatic sites. Three patients had received prior therapy: 1 had prior cytokine and targeted therapy (temsirolimus), 1 had targeted therapy (temsirolimus), and 1 received chemotherapy. Non-clear cell histologies included 8 (35%) papillary, 2 (9%) chromophobe, 4 (17%) collecting duct, 1 (4%) medullary, 5 (22%) unclassified and 3 (13%) had hereditary leiomyomatosis and renal cell cancer-related RCC (HLRCC). Genetic testing for HLRCC was performed on 1 out of 3 HLRCC-related tumors. One of the patients with unclassified histology had a possible translocation-associated RCC. Sarcomatoid features were present in 3 (2 collecting duct and 1 unclassified) out of the 23 patients.

Papillary RCC patients and other rare non-clear cell histology patients were analyzed separately. Descriptive statistics were provided on patient characteristics, toxicities, and responses. Kaplan-Meier method [20] was used to estimate progression free survival (PFS)

Response

One patient discontinued protocol treatment due to toxicity prior to completion of cycle 1, leaving 22 patients evaluable for response (Table 1). One patient with unclassified RCC achieved a partial response to sunitinib treatment. The patient progressed after 36 weeks of therapy. Fifteen (65%) had a best response of stable disease (SD). One patient with SD remains on therapy after 48 weeks. The remaining 14 patients with SD developed progressive disease on treatment. Six (26%) patients were noted to have progressive disease at their first reassessment. For each of the 22 evaluable patients, the maximum reduction in tumor size during treatment and RCC histology are displayed in Fig. 1. PFS was assessed in all 23 patients from start of sunitinib therapy (Fig. 2). The median PFS was 5.5 months (95% CI, 2.5–7.1). Similarly, the median PFS for the 8 papillary patients was 5.6 months (95% CI, 1.4–7.1).

Toxicity

All twenty three (100%) patients were evaluable for toxicity. In general, the treatment was well tolerated. The most common toxicities are listed in Table 2; the safety profile was compatible with prior reports [13].

Discussion

The primary objective of this phase II clinical trial was to assess the overall response rate for sunitinib in patients with papillary mRCC as well as other non-clear cell histologies. Only 1 partial response was observed in a patient with unclassified mRCC, and no objective responses were observed in patients with papillary mRCC. The robust activity of sunitinib in producing objective responses in patients with clear cell RCC [7, 13, 21] was lacking in this study comprised of patients with non-clear cell histologies.

Our findings are consistent with recent reports citing few responses to treatment with sunitinib in subsets of patients with non-clear cell histologies [22, 23]. One phase II study of sunitinib therapy in non-clear cell histologies recently reported no major responses, a median PFS of 1.6 months (95% CI, 1.3–12), and OS of 10.8 months (95% CI, 6.2–NE) in a subset of papillary patients [24]. More encouraging results in patients with non-clear cell histologies have been observed with agents targeting pathways other than VEGF. For example, in a large phase 3 trial, the mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, demonstrated a significant survival benefit over interferon in patients with metastatic RCC of any histology. In fact, in a subset analysis, the benefit appeared to be more significant in patients with non-clear-cell histology [5]. Similarly, an 11% objective response rate was achieved in a recent study assessing the epidermal growth factor receptor

(EGFR) inhibitor, erlotinib, in 45 patients with papillary RCC [25]. These agents may therefore hold more promise (both alone or as part of combination regimens) than the VEGF pathway inhibitors for patients with non-clear cell RCC.

In summary, non-clear cell histologies represent an uncommon and heterogeneous group of RCC for which effective treatments have not yet been found. The study of novel agents and identification of specific targets in these RCC groups is a direction for the future.

Abbreviations

mRCC	Metastatic renal cell carcinoma
RCC	Renal cell carcinoma
HLRCC	Hereditary leiomyomatosis and renal cell cancer
CTCAE	Common toxicity criteria for adverse events
RECIST	Response evaluation criteria in solid tumors

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Fig. 1.
Maximal percentage of tumor reduction for target lesions by Response Evaluation Criteria in Solid Tumors (RECIST)

Fig. 2.
Progression-free survival ($N = 23$)

Table 1Patient characteristics and best responses to sunitinib treatment ($N = 23$)

Characteristic	Papillary ($N = 8$)	Other non-clear cell ($N = 15$)	All patients	
			($N = 23$)	%
Sex				
Male	7	10	17	74
Female	1	5	6	26
Age, y				
Median (range)	69 (35 to 80)	53 (21 to 72)	55 (21 to 80)	
Race				
White non-Hispanic	6	12	18	78
Black non-Hispanic	1	2	3	13
Other	1	1	2	9
Prior nephrectomy	6	12	18	78
Prior systemic treatment				
Interferon-alfa	1	0	1	4
Temsirolimus	1	1	2	9
Cisplatin/gemcitabine	0	1	1	4
Histology subtype				
Papillary	8	–	8	35
Chromophobe	–	2	2	9
Collecting duct	–	4	4	17
Medullary	–	1	1	4
Unclassified	–	5	5	22
HLRCC-related	–	3	3	13
Sites of metastatic disease				
Lung	5	5	10	43
Liver	0	2	2	9
Bone	0	1	1	4
Lymph nodes	7	12	19	83
Other	2	9	11	48
No. of metastatic sites				
1	3	4	7	30
≥2	5	11	16	70
Karnofsky performance status (%)				
80	1	4	5	22
90	7	11	18	78
MSKCC risk group [14]				
Favorable	3	9	12	52
Intermediate	5	5	10	44
Poor	0	1	1	4
Best response to sunitinib				

Characteristic	Papillary (N = 8)	Other non-clear cell (N = 15)	All patients	
			(N = 23)	%
Partial response	0	1	1	4
Stable disease	6	9	15	65
Progressive disease	2	4	6	26
Not evaluable	0	1	1	4

Table 2Laboratory abnormalities and selected treatment-emergent adverse events in response to sunitinib ($N = 23$)

Adverse event	Number of patients				Total	%
	Grade 1	Grade 2	Grade 3	Grade 4		
Anemia	11	6	3	1	21	91
Leukopenia	6	9	1	0	16	70
Lymphopenia	0	0	5	0	5	22
Thrombocytopenia	14	4	1	0	19	83
Neutropenia	0	9	1	0	10	43
Elevated ALT	12	3	2	0	17	74
Elevated AST	11	5	0	0	16	70
Elevated alkaline phosphatase	11	3	0	0	14	61
Elevated creatinine	10	2	3	0	15	65
Hyperkalemia	7	3	2	0	12	52
Fatigue	8	3	0	0	11	48
Diarrhea	6	0	0	0	6	26
Mucositis	8	0	1	0	9	39
Vomiting	7	0	0	0	7	30
Thrombosis	0	0	0	2	2	9
Hypertension	4	1	1	0	6	26
Skin (rash, hand-foot skin reaction and other)	8	0	3	0	11	48