Published in final edited form as:

Clin Genitourin Cancer. 2013 September ; 11(3): 297–302. doi:10.1016/j.clgc.2013.04.001.

Long-Term Response to Sunitinib Therapy for Metastatic Renal Cell Carcinoma

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Abstract

A subset of patients achieves long-term responses with sunitinib therapy. We present a retrospective study of long-term responders, defined as patients achieving durable complete response (CR) or remaining progression free for > 18 months while receiving sunitinib. Favorable risk factors associated with long-term response include a lack of bone metastases or lung metastases and favorable Memorial Sloan-Kettering Cancer Center (MSKCC) risk status.

Background—Sunitinib achieves objective response and prolongs progression-free survival (PFS) in patients with metastatic renal cell carcinoma (RCC). A subset of patients achieves long-term responses. The characteristics of patients who achieved long-term response (defined as patients achieving ongoing complete response [CR] or remaining progression free for > 18 months while receiving sunitinib) are reported.

Patients and Methods—A database of 186 patients treated with sunitinib alone (n = 89) or in combination (n = 97) in 9 clinical trials was reviewed; all had 1 year or more follow-up from sunitinib start to data cutoff for analysis. Median PFS was 10.8 months (95% CI, 8.3–13.3); median overall survival (OS) was 30.4 months (95% CI, 21.5–36.8 months) for the 186 patients. Thirty-four patients were identified as long-term responders because they either had durable CR or remained progression free while receiving sunitinib for > 18 months.

Results—Best response for 34 long-term responders was CR in 3 patients, partial response (PR) in 24 patients, and stable disease in 7 patients. The median duration of sunitinib therapy was 24.9 months (range, 18.1–73.9 months). The median PFS among the long-term responders was 17.4 months (95% CI, 7–29.9 months) at a landmark PFS analysis performed after 18 months from

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Disclosure

Dr Motzer has received research funding from and is a consultant for Pfizer.

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treatment start. Univariate analysis from the 186 patients identified bone metastasis, lung metastasis, and intermediate/poor risk groups as adverse prognostic factors for long-term response.

Conclusion—Sunitinib achieves long-term response in a subset of patients with metastatic RCC. Lack of bone metastasis or lung metastasis and good MSKCC risk status may predict long-term response.

Keywords

Metastatic; Renal cell carcinoma; Sunitinib; Systemic therapy; Targeted therapy

Introduction

Metastatic clear cell renal cell carcinoma (RCC) is highly resistant to conventional chemotherapy. Approximately one third of patients present at initial diagnosis with evidence of metastases, and disease in 20% to 40% of patients relapses after nephrectomy. Recently, advances in the understanding of the biological characteristics of RCC have facilitated the development and implementation of novel targeted therapies in the treatment paradigm for metastatic RCC. Small-molecule targeted inhibitors demonstrated antitumor activity in randomized phase III clinical trials and have assumed a predominant role in standard management for metastatic RCC.^{1–7}

Sunitinib malate, a multitargeted inhibitor of receptor tyrosine kinases, has established efficacy in the treatment of metastatic RCC. Two phase II trials and a phase III trial showed that sunitinib therapy achieved response rates between 30% and 50%, and median progression-free survival (PFS) of 11 months was found in a first-line phase III trial.^{1,2,8,9} From experience at our center, we have observed that a subset of patients achieve long-term responses with sunitinib therapy. To describe the features of these patients, a retrospective analysis was performed of all patients with metastatic RCC treated with sunitinib in clinical trials. We report on clinical features, treatment outcomes, and survival for long-term responders, defined as patients achieving durable complete response (CR) or remaining progression free for > 18 months while receiving sunitinib. In addition, we report on the entire cohort of patients treated in sunitinib clinical trials and provide comparisons.

Patients and Methods

One hundred eighty-six patients with metastatic RCC, enrolled in 9 clinical trials approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Board Review at MSKCC between January 2003 and December 2008, were included in this retrospective study.^{1,8–14} Patients received sunitinib monotherapy in 6 trials and combination therapy with sunitinib plus gefitinib, bevacizumab, or everolimus in 3 trials. All patients had findings of RCC histologic type by pathologic review at MSKCC, clinical evaluation showing metastases, and follow-up data.

The entry point for study was defined as the date of first treatment for patients treated in a prospective sunitinib clinical trial. Patients who had been treated in > 1 clinical trial were evaluated for this study at the time of entry into the first MSKCC trial. Patient demographics, clinical features at study entry, systemic therapy, assessment of response, date of last follow-up, and status were recorded. The χ^2 test was used to compare the distribution of categorical baseline characteristics of the long-term responders and the remainder of the patients identified as short-term responders. The Wilcoxon rank-sum test was used to compare the distributions of age between the 2 groups. PFS was measured in months from the start of therapy to first documentation of objective disease progression or to death from any cause, whichever occurred first. Overall survival (OS) was measured in

months from the start of therapy to the date of death or last follow-up. Both PFS and overall survival during follow-up were estimated by Kaplan-Meier methodology.¹⁵ PFS analysis was performed at a landmark time point 18 months after the start of therapy. The purpose of the landmark analysis was to estimate the additional progression-free duration among patients who were able to continue sunitinib therapy without progression for 18 months. We call these patients *long-term responders*. A landmark analysis was performed to focus on the outcomes of long-term responders. Patients were included in the analysis if (1) they experienced the event of interest before the landmark time or (2) they had complete follow-up until or beyond the landmark time. Time 0 for a landmark time-to-event analysis starts at the landmark time (in this analysis 18 months) so that the resulting Kaplan-Meier survival estimates are not biased.^{16,17} Eighteen months represented between 1.5 and 2 times the median PFS from the pivotal sunitinib and COMPARZ studies and provided a reasonable number of patients for analysis.^{1,18} In addition, logistic regression was performed on all patients to evaluate the effect of each clinical variable on the probability of responding long term. One patient who was lost to follow-up before 18 months was excluded from this analysis.

Results

Patient Characteristics and Treatment

Between January 2003 and December 2008, a total of 186 patients enrolled in clinical trials at MSKCC. Thirty-four of 186 patients were identified as long-term responders. Table 1 shows the baseline characteristics for the long-term and short-term responders. Both groups were similar regarding sex, median age, and race. Clear cell carcinoma was the predominant histologic type, accounting for 91% of the long-term and 87% of the short-term responders. The majority of patients in the entire cohort had undergone nephrectomy before initiating systemic therapy. In addition, the majority of patients had 2 or more metastatic sites. The proportion of patients with lung metastases was higher in the short-term responders than in the long-term responders (74% vs. 53%; $P = .02$). The distribution of patients by MSKCC risk group showed a higher proportion of patients with favorable risk status in the long-term response group (65% vs. 45%; $P = .05$).¹⁹

Treatment and Adverse Events

Sunitinib was administered to the 186 patients as monotherapy in 6 trials (89 patients) or as part of a combination program (97) in 3 trials, with gefitinib, bevacizumab, or everolimus. The median duration of treatment with sunitinib was 6.4 months (range, 0.03–73.9 months) for these 186 patients. Among the 34 long-term responders who received sunitinib treatment for at least 18 months, the median duration of treatment was 24.9 months (range, 18.1–73.9 months). Of the 34 long-term responders, 27 received sunitinib monotherapy and 7 received combination therapy with gefitinib ($n = 4$), everolimus ($n = 2$), or bevacizumab ($n = 1$). Over the course of treatment, 13 long-term responders (38%) had dose reductions of 1 dose level (ie, 50 mg to 37.5 mg or 37.5 mg to 25 mg) at 18 months compared with the remaining 21 patients (62%) who remained on the same treatment doses as baseline. All long-term responders (34 patients) were evaluated for grade 3 and 4 treatment-emergent adverse events (AEs) over the course of their therapy, in many instances after completion of “protocol therapy.” The onset and occurrence of AEs specified as occurring before 18 months and after 18 months were tabulated. Commonly reported grade > 3 AEs included fatigue, diarrhea, hypertension, and hand-foot syndrome (Table 2). The most commonly reported laboratory grade > 3 AEs included lymphopenia, neutropenia, and hypophosphatemia (Table 2). Unique late grade 3 or 4 AEs that developed beyond 18 months of treatment were not identified.

Response

Among the 186 patients in the data set, 180 patients were evaluable for response. Seventy-eight (43%) achieved objective responses: 4 CRs and 74 partial responses (PRs). Eighty patients achieved stable disease as their best response. Among the 34 patients categorized as long-term responders, 27 (79%) achieved objective responses: 3 CRs and 24 PRs (Table 3). Seven patients achieved stable disease as their best response.

The median OS in the 186 sunitinib-treated patients was 30.4 months (95% confidence interval [CI], 21.5–36.8 months) (Figure 1A). At the time of analysis, 152 of the 186 patients and 24 of the 34 long-term responders had died.

PFS and OS were assessed in the entire cohort of patients. The median PFS was 10.8 months (95% CI, 8.3–13.3) (Figure 1B). A landmark PFS analysis was performed at 18 months for the long-term responders (Figure 2). The median PFS at this landmark time was 17.4 months (95% CI, 7–29.9). Described in another way, after 18 months of being progression free, long-term responders had a median PFS of 17.4 months.

Risk Factors

Logistic regression analyses were performed on the entire cohort of 186 patients to assess the associations between risk factors of interest and whether a patient was defined as being a long-term responder. Risk factors assessed included sites of metastases, number of metastatic sites, histologic type, performance status, MSKCC risk group, and whether previous therapy was given. The odds ratio (OR) estimate for each variable is listed in Table 4. Long-term responders had a lower odds of having a bone metastasis (OR, 0.41; 95% CI, 0.15–1.12; $P = .08$), of having lung metastasis (OR, 0.39; 95% CI, 0.18–0.84; $P = .02$), and a greater odds of being in the favorable risk group (OR, 2.21; 95% CI, 1.02–4.78; $P = .045$) compared with short-term responders.

Discussion

Sunitinib is standard first-line therapy for metastatic RCC based on results of a phase III clinical trial that showed longer PFS and response rates in patients who received sunitinib than in patients who received interferon alfa.²⁰ In the final survival analysis and updated results of this trial, sunitinib compared with interferon alfa demonstrated longer OS (26.4 vs. 21.8 months; $P = .051$) and improvement in response rate (47% vs. 12%; $P < .05$) and PFS (11 vs. 5 months; $P < .05$).²

In this report of patients treated with sunitinib in multiple clinical trials, we identified a subset of long-term responders defined as patients achieving ongoing CR or remaining progression free while receiving sunitinib for > 18 months. This cohort achieved an objective response rate of 79%, with 3 patients achieving CR solely with medical therapy. Median PFS was 17.4 months on a landmark PFS analysis performed after 18 months from treatment start.

Patients remained on sunitinib therapy a median of 24.9 months, with the longest duration being 73.9 months. The safety profile of sunitinib therapy was compatible with previous reports, without unique late toxicities beyond 18 months of treatment identified.^{2,21} Treatment dose reductions occurred in 13 (38%) of the patients in our study.

In our study, risk factors associated with long-term response included lack of bone metastases or lung metastases and favorable MSKCC risk status. Heng et al identified patients who achieved CR with sunitinib treatment as more likely to have favorable or

intermediate MSKCC risk.²² In addition, patients had significant reductions in composite tumor measurements within the first 2 cycles of treatment. Others have not been able to identify clinical or biological parameters associated with long-term responses or complete remissions.²³

One issue that has arisen as a result of favorable treatment outcome with sunitinib is whether systemic therapy should be maintained or discontinued at a certain time point in patients with long-term responses or CR. Ayllon et al advocate that surgical resection of metastases in responding patients can eradicate metastatic disease and avoid unnecessary toxicity and high costs of chronically administered antiangiogenic therapy.²⁴ Complete remissions with antiangiogenic therapy are rare, and when they occur in the setting of metastasectomy, durable CR is often not achieved.^{23–27} In a recent multicenter retrospective analysis, Albiges et al identified 64 patients who achieved CR during treatment with tyrosine kinase inhibitors either alone or with local treatment (ie, surgery, radiotherapy, or radiofrequency ablation).²⁴ None of the patients who received surgery with pathologic review achieved a durable CR.

Data on patient outcomes subsequent to treatment discontinuation after response, although limited, indicate that recurrences are frequent.^{23,27–29} In a retrospective study, Johannsen et al reported relapses in 24 of 36 patients (66.7%) who discontinued targeted therapy after achieving CR from systemic therapy alone or after metastasectomy.²⁷ Most patients experienced relapses at the site of existing disease, and new metastatic sites were identified in 3% of these patients. Likewise, others have also reported disease recurrence after treatment discontinuation.^{28,29} There have been reports that select patients who relapse after drug discontinuation remain sensitive to targeted therapy, many to the same tyrosine kinase inhibitor that induced the initial CR.²³ Predictive variables associated with time to recurrence/progression after discontinuation of targeted therapy have not been identified in either univariate or multivariable adjusted models.²⁷ In our study, 1 of 3 patients remained in CR 18 months after drug discontinuation. One patient experienced progression while receiving therapy for 45 months after achieving CR, and 1 patient experienced progression 48 months after drug discontinuation.

Based on the data available, treatment discontinuation after long-term response or complete remission is generally not recommended. Pathologic CR is rare, arguing for the need to continue systemic therapy to treat residual disease.

Conclusion

In summary, sunitinib achieves long-term response in a subset of patients with metastatic RCC. Lack of bone metastasis or lung metastasis and good MSKCC risk may predict long-term response. Long-term treatment with sunitinib is well tolerated. Optimal management of long-term responders regarding duration of therapy and surgical resection of metastases in responding patients remain important issues in patient management.

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Clinical Practice Points

- A subset of patients with metastatic RCC achieves long-term responses with sunitinib therapy.
- In this retrospective analysis, we report on long-term responders, defined as patients achieving durable CR or remaining progression free for 18 months while receiving sunitinib therapy.
- Risk factors associated with long-term response include lack of bone metastases, lack of lung metastasis, and favorable MSKCC risk status.
- Long-term treatment for 18 months with sunitinib is well tolerated.

Figure 1.
 (A) Overall Survival. (B) Progression-Free Survival for All Patients

Figure 2.
Landmark Progression-Free Survival for Long-Term Responders

Table 1

Patient Characteristics

Variable	All Patients (n = 186) ^a	Long-Term Response (n = 34)	Short-Term Response (n = 151)	P Value
Sex, No. (%)				
Male	124 (67)	26 (76)	98 (65)	.19
Female	62 (33)	8 (24)	53 (35)	
Age, y				
Median (range)	61 (23–81)	61 (40–73)	62 (23–81)	.21 ^b
Race (%)				
White non-Hispanic	176 (95)	34 (100)	141 (93)	.23
Black non-Hispanic	3 (1.6)	0	3 (2)	
Other	7 (4)	0	7 (5)	
Previous Nephrectomy, No. (%)	149 (80)	26 (76)	122 (81)	.83
No. of Disease Sites, No. (%)				
1	46 (25)	12 (35)	33 (22)	.12
2	140 (75)	22 (65)	118 (78)	
Sites of Metastases, No. (%)				
Lung	131 (70)	18 (53)	112 (74)	.02
Mediastinum	31 (17)	7 (21)	24 (16)	.61
Retroperitoneal lymph nodes	15 (8)	2 (6)	13 (9)	1
Bone	50 (27)	5 (15)	45 (31)	.09
Liver	41 (22)	4 (12)	37 (25)	.12
Lymph nodes	86 (46)	15 (44)	70 (46)	.85
Other	60 (32)	12 (35)	48 (32)	.69
Histologic Subtype, No. (%)				1
Clear cell	164 (88)	31 (91)	132 (87)	
Papillary	7 (4)	1 (3)	6 (4)	
Chromophobe	5 (3)	1 (3)	4 (3)	
Unclassified	6 (3)	1 (3)	5 (3)	
MSKCC Risk Group (%)¹⁹				.05
Favorable	91 (49)	22 (65)	68 (45)	
Intermediate	87 (47)	10 (29)	77 (51)	
Poor	8 (4)	2 (6)	6 (4)	

Abbreviation: MSKCC = Memorial Sloane-Kettering Cancer Center.

^aOne patient was lost to follow-up without experiencing progression before 18 months; hence, long-term status cannot be determined.

^bP value is generated using Wilcoxon rank-sum test.

Table 2

Toxicities for Long-Term Responders (n = 34)

Clinical Toxicity	All (n = 34)		Onset < 18 mo		Onset > 18 mo	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	4		3		3	—
Diarrhea	7		4		3	—
Hypertension	3		2		1	—
Nausea	1		1		—	—
Vomiting	2				2	—
Rash, Hand-Foot Skin Reaction	5		4		2	—
Fever (in the Absence of Neutropenia)	1		1		—	—
Hemorrhage	2		2		—	—
Anemia	4		1		4	—
Neutropenia	5		3		4	—
Lymphopenia	12	1	9		5	1
Increased AST Level	1		1		—	—
Increased ALT Level	5		3		2	—
Hypophosphatemia	9	1	7	1	5	
Proteinuria	1	—	—	—	1	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Table 3

Summary of Efficacy Measures

Variable	All (N = 186) ^a	Long-Term Responders (n = 34)
Best Objective Response		
Complete response	4 (2%)	3 (9%)
Partial response	74 (40%)	24 (71%)
Stable disease	80 (43%)	7 (21%)
Disease progression	22 (12%)	0
Overall Survival		
Number of deaths	152 (82%)	24 (71%)

^a Six patients were not evaluable.

Table 4

Univariate Analysis

	All (N = 186)	Long-Term Responders (n = 34)	Univariate Logistic Analysis (Yes vs. No) Odds Ratio (95% CI)	P Value
Site of Disease				
Bone	50 (27%)	5 (15%)	0.41 (0.15–1.12)	.08
Lung	131 (70%)	18 (53%)	0.39 (0.18–0.84)	.02
Liver	41 (22%)	4 (12%)	0.41 (0.14–1.26)	.12
> 2 Metastatic Sites	140 (75%)	22 (65%)	0.53 (0.24–1.19)	.12
Previous Treatment	72 (39%)	15 (44%)	1.32 (0.62–2.79)	.48
Clear Cell Histologic Type	164 (88%)	31 (91%)	1.48 (0.41–5.30)	.55
MSKCC Risk Group				
Favorable	91 (49%)	22 (65%)	2.21 (1.02–4.78)	.045
Intermediate/poor	95 (51%)	12 (35%)	1.0 (reference)	