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Sunitinib objective response in metastatic renal cell carcinoma: Analysis of 1059 patients treated on clinical trials

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Article Outline

Abstract

Background

Retrospective analyses were performed in patients with metastatic renal cell carcinoma (mRCC) to characterise the objective response (OR) rate to sunitinib and differentiate pretreatment features and outcomes of patients with early (response by ≤12 weeks) versus late response, and responders versus non-responders.

Methods

Data were pooled from 1059 patients in six trials. Median progression-free survival (PFS) and overall survival (OS) were estimated by Brookmeyer and Crowley method and compared between groups by log-rank test. Baseline characteristics were compared by Fisher-exact, *t*-, or Wilcoxon rank-sum tests. Associations between characteristics and survival were investigated by Cox proportional regression analysis.

Results

398 patients (38%) had confirmed OR (12 complete responses); 26%, 61%, 79% and 86% responded by 6, 12, 18 and 24
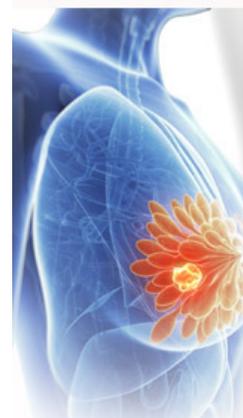
weeks, respectively. Median (range) time to tumour response (TTR) was 10.6 (2.7–94.4) weeks and was similar in treatment-naïve and cytokine-refractory patients. Median response duration in early and late responders was 52.0 and 55.0 weeks, respectively. Median PFS in early versus late responders was 13.8 versus 20.2 months ($P = 0.001$); however, median OS did not significantly differ (37.8 versus 40.8 months; $P = 0.144$). Early responders had more lung metastases ($P < 0.01$), but baseline characteristics were otherwise mostly similar. Median PFS (16.3 versus 5.3 months) and OS (40.1 versus 14.5 months) were longer in responders versus non-responders (both $P < 0.001$); responders had more favourable prognostic factors.

Conclusions

OR occurred in 38% of sunitinib-treated mRCC patients. Sixty-one percent of responses occurred by 12 weeks of therapy, and responders had favourable pretreatment features and significantly longer survival.

Keywords: Sunitinib, Objective response, Metastatic renal cell carcinoma

Back to Article Outline

1. Introduction

Targeted therapies may have both a cytotoxic and a cytostatic effect, complicating assessment of response to treatment [1], [2]. It is unclear to what extent the achievement of a tumour objective response (OR), or its timing, contributes to survival outcomes. This has led to the study of alternative functional and molecular imaging techniques to augment conventional size-based measurement of tumour response (i.e. response based on Response Evaluation Criteria in Solid Tumours [RECIST] [3]) in order to account for disease stabilisation [1], [2].

Sunitinib malate (SUTENT®; Pfizer, New York, NY) is an orally administered, multi-targeted inhibitor of receptors for vascular endothelial growth factor (VEGF), platelet-derived growth factor and other tyrosine kinases [4] that has been approved worldwide for the treatment of advanced renal cell carcinoma (RCC). The efficacy and safety of sunitinib as first-line and cytokine-refractory treatment of metastatic renal cell carcinoma (mRCC) have been established in six key clinical trials, in which robust OR rates were achieved (20–47%) [5], [6], [7], [8], [9], [10]. In a pivotal phase III study of treatment-naïve patients with mRCC, sunitinib significantly improved progression-free survival (PFS) versus interferon-alfa (11 versus 5 months, respectively; $P < 0.001$) and prolonged median overall survival (OS) to more than 2 years [8].

Despite potential limitations to using tumour response, prior studies of sunitinib in patients with mRCC have indicated that both early reductions in primary tumour size and best response with sunitinib are predictive of improved survival. A retrospective study of 75 patients with mRCC found that a 10% or greater decrease in primary tumour size within 60 days of treatment initiation was independently associated with a 74% decreased risk of death ($P = 0.031$) [11]. In a retrospective study of 55 sunitinib-treated patients with mRCC (in which Choi- and RECIST-based criteria for tumour response were assessed), RECIST-defined best response was significantly associated with median PFS and OS ($P \leq 0.001$) [12]. However, these studies were small and/or hypothesis generating, warranting confirmation in a larger patient dataset.

Using pooled data from 1059 patients with mRCC treated with sunitinib in six clinical trials, retrospective analyses was performed to characterise the OR rate with sunitinib and differentiate pretreatment features and outcomes of patients with early (response by ≤12 weeks) versus late response, and responders versus non-responders.

Back to Article Outline

2. Patients and methods

2.1. Patients

Patients were ≥18 years of age with the following eligibility criteria: histologically confirmed mRCC, evidence of measurable disease according to RECIST [3], no known presence of brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (or Karnofsky performance status ≥70 in one trial [10]), and adequate organ function.

2.2. Study design and treatments

In the six prospective clinical trials from which pooled data were used for these retrospective analyses (five phase II trials and one phase III trial), sunitinib was administered orally at a starting dose of either 50 mg/day for 4 consecutive weeks followed by 2 weeks off treatment in repeated 6-week cycles (Schedule 4/2; $n = 690$; 65%) or 37.5 mg/day on a continuous once-daily dosing schedule ($n = 369$; 35%). To date, it has been shown that response rates are comparable in patients with mRCC who receive sunitinib on either Schedule 4/2 or continuous daily dosing [10], thus justifying use of pooled data from patients on either schedule. Sunitinib was administered in either the first-line ($n = 783$; 74%) or the cytokine-refractory ($n = 276$; 26%) treatment setting. Treatment continued until disease progression, lack of clinical benefit, unacceptable toxicity or withdrawal of consent.

Antitumour efficacy end-points employed in the six trials included OR rate and PFS (both assessed by investigators using RECIST [3]) and OS. Tumour response was assessed according to the schedules specified in the protocols of each trial (initially every 4–6 weeks, increasing to every 8–12 weeks after approximately 6 months). Adverse events were recorded regularly and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (version 2.0 in one trial [5]).

The studies were run in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines (or the Declaration of Helsinki) and applicable local regulatory requirements and laws, and approved by the institutional review boards or independent ethics committees of each participating centre (ClinicalTrials.gov: NCT00267748, NCT00137423, NCT00083889, NCT00077974, NCT00054886, NCT00338884).

2.3. Statistical methods

Median PFS and OS were estimated by the Brookmeyer and Crowley method and compared between early versus late responders (first observed response [confirmed at next visit] at ≤12 versus >12 weeks, respectively), and responders versus non-responders, by log-rank test. Hazard ratios for these comparisons were calculated using a Cox proportional-hazards model.

Baseline characteristics for early versus late responders, and responders versus non-responders, were compared by Fisher-exact test, *t*-test or Wilcoxon rank-sum test.

A Cox proportional regression model was used to analyse the associations between PFS and OS in each group and potential prognostic factors. Each variable was investigated by univariate and then multivariate analysis in a step-wise procedure, in which factors with $P < 0.2$ by Wald chi-square test were included in the multivariate analysis. Further elimination was applied within the multivariate analysis to identify independent variables significant at $P < 0.05$. The covariates analysed included objective tumour response (yes/no), time on treatment and baseline pretreatment characteristics comprised of prognostic factors reported by the Memorial Sloan-Kettering Cancer Center (MSKCC) [13] and Heng et al. [14] as well as prior cytokine treatment (yes/no) and presence/absence of lung and bone metastases.

The Cox proportional-hazards model was repeated using a 12-week landmark for the occurrence of a response in order to address potential bias resulting from assessment of survival in patients with disproportionate treatment duration. Hence, for purposes of this landmark analysis, if a patient had his/her first response after 12 weeks, then he/she was classified as a non-responder.

A logistic regression analysis of response as function of relative dose intensity and other covariates was also conducted.

Back to Article Outline

3. Results

3.1. Patients with objective response (responders)

A total of 1059 patients with mRCC were treated with sunitinib: 398 (38%) had a confirmed OR, including 12 with a complete response, as assessed by investigators according to RECIST. Median time to tumour response (TTR) was 10.6 weeks (range 2.7–94.4 weeks), which was similar in the first-line and cytokine-refractory treatment settings. Among patients with OR, 105 (26%), 243 (61%), 314 (79%) and 342 (86%) responded by 6, 12, 18 and 24 weeks, respectively.

3.2. Early versus late responders

Two hundred and forty-three of the 398 responders (61%) had a tumour response by ≤12 weeks and, for purposes of this analysis, were therefore categorised as early responders, compared with 155 responders (39%) who had a response after >12 weeks and were defined as late responders. The proportion of early versus late responders was similar regardless of treatment setting.

Compared with late responders, early responders were younger, had a shorter interval since initial diagnosis and had more lung metastases (all $P < 0.05$; Table 1). Tumour burden at baseline was similar in the two groups. These differences in baseline characteristics were broadly similar in each treatment setting, although the interval since initial diagnosis was very similar in early and late responders in the cytokine-refractory setting.

Table 1. Baseline patient characteristics of early versus late responders to sunitinib.

Characteristic	Early responders[a] (*n* = 243)	Late responders[a] (*n* = 155)	*P* value
Median (range) age, years	59 (35–81)	63 (32–87)	0.006
Male/female, %	73/27	68/32	0.365
ECOG performance status, *n* (%)			
0	172 (71)	107 (69)	0.712
1	68 (28)	46 (30)	
2	3 (1)	2 (1)	
Risk factors based on published MSKCC data, *n* (%)[b]			
0 (favourable)	130 (53)	86 (55)	0.732
1–2 (intermediate)	82 (34)	50 (32)	
⩾3 (poor)	6 (2)	2 (1)	
Missing	25 (10)	17 (11)	
Mean time (range) since initial diagnosis, years	2.4 (0–20.1)	3.9 (0–25.3)	0.001
Histology, *n* (%)			

Characteristic	Early responders[a] (*n* = 243)	Late responders[a] (*n* = 155)	*P* value
Clear cell	236 (97)	152 (98)	0.747
Non-clear cell	7 (3)	3 (2)	
Prior nephrectomy, *n* (%)[c]	201 (83)	132 (85)	0.534
Prior cytokine therapy, *n* (%)	64 (26)	37 (24)	0.637
Sites of metastatic disease, *n* (%)			
Lung	203 (84)	108 (70)	0.002
Liver	55 (23)	35 (23)	1.0
Bone	66 (27)	29 (19)	0.055
Median (range) tumour burden, mm	83 (10–481)	85 (10–432)	0.803

ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center.

[a]Early and late responders were defined by tumour response at ≤12 and >12 weeks, respectively.

[b]Includes low serum haemoglobin level, elevated corrected serum calcium level, elevated serum lactate dehydrogenase level, poor performance status and interval of <1 year between diagnosis and sunitinib treatment [13].

[c]Nephrectomy status missing for 15 patients (4%).

Median duration of response was similar in early and late responders in the overall population, as well as in the first-line setting (Table 2). However, in the cytokine-refractory setting, median duration of response appeared shorter in early compared with late responders (Table 2). The reduction in tumour burden was similar in early and late responders, regardless of treatment setting (Table 2).

Table 2. Response duration and percent reduction in size of disease by treatment setting in early and late responders to sunitinib.

|	All responders		Treatment-naïve responders		Cytokine-refractory responders	
	Early[a] (*n* = 243)	Late[a] (*n* = 155)	Early[a] (*n* = 181)	Late[a] (*n* = 120)	Early[a] (*n* = 62)	Late[a] (*n* = 35)
Median response duration, weeks	52.0	55.0	56.1	55.0	43.0	55.0
Mean (SD) reduction, %	61.85 (20.33)	56.24 (18.56)	62.58 (20.46)	56.32 (18.52)	59.77 (19.94)	55.96 (18.95)
Median (range) reduction, %	58.52 (21.43–100)	52.46 (30.96–100)	59.14 (21.43–100)	53.38 (31.75–100)	55.92 (31.25–100)	51.96 (30.96–98.58)

SD, standard deviation.

[a]Early and late responders were defined by tumour response at ≤12 and >12 weeks, respectively.

Median PFS was significantly shorter in early versus late responders (13.8 versus 20.2 months, respectively; *P* = 0.001; Fig. 1A); however, OS did not significantly differ (37.8 versus 40.8 months, respectively; *P* = 0.144; Fig. 1B). Results were similar regardless of treatment setting (data not shown).

The proportion of patients who discontinued sunitinib treatment because of an adverse event was similar in early and late responders in the overall population (13% versus 17%, respectively) and in the first-line treatment setting (15% versus 16%); however, in the cytokine-refractory setting, early responders discontinued less frequently than late responders (8% versus 20%).

3.3. Responders versus non-responders
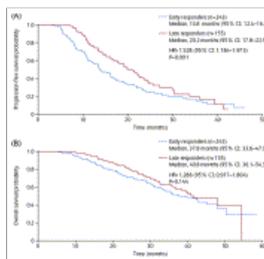
Fig. 1.

Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival in early versus late responders to sunitinib.

Responders had significantly better performance status, more favourable risk factor classification based on published MSKCC criteria, a longer interval since initial diagnosis, higher rates of nephrectomy and a lower incidence of bone metastases (all P < 0.05; Table 3). The characteristics of responders were generally maintained regardless of treatment setting, although, in the cytokine-refractory setting, there were no significant differences by response status in time since initial diagnosis or rates of prior nephrectomy.

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Table 3. Baseline patient characteristics of responders versus non-responders to sunitinib.

Characteristic	Responders (n = 398)	Non-responders (n = 661)	P value
Median (range) age, years	61 (32–87)	60 (24–87)	0.317
Male/female, %	71/29	70/30	0.628
ECOG performance status, n (%)			
0	279 (70)	368 (56)	<0.001
1	114 (29)	276 (42)	
2	5 (1)	17 (3)	
Risk factors based on published MSKCC data, n (%)[a]			
0 (favourable)	216 (54)	200 (30)	<0.001
1–2 (intermediate)	132 (33)	282 (43)	
⩾3 (poor)	8 (2)	37 (6)	
Missing	42 (11)	142 (21)	
Mean time (range) since initial diagnosis, years	3.0 (0–25.3)	2.2 (0–28.3)	0.002
Histology, n (%)[b]			
Clear cell	388 (97)	639 (97)	0.515
Non-clear cell	10 (3)	19 (3)	
Prior nephrectomy, n (%)[b]	333 (84)	500 (76)	0.012
Prior cytokine therapy, n (%)[b]	101 (25)	189 (29)	0.256
Sites of metastatic disease, n (%)			
Lung	311 (78)	509 (77)	0.761
Liver	90 (23)	156 (24)	0.764
Bone	95 (24)	216 (33)	0.002

ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center.

aIncludes low serum haemoglobin level, elevated corrected serum calcium level, elevated serum lactate dehydrogenase level, poor performance status and interval of <1 year between diagnosis and sunitinib treatment [13].

bHistology data missing for three patients (<1%), nephrectomy status missing for 57 patients (5%), and prior cytokine status missing for one patient (<1%).

Median PFS was significantly longer in responders versus non-responders (16.3 versus 5.3 months, respectively; $P < 0.001$; Fig. 2A), as was median OS (40.1 versus 14.5 months, respectively; $P < 0.001$; Fig. 2B). Survival outcomes were improved in responders compared with non-responders regardless of treatment setting (Table 4).
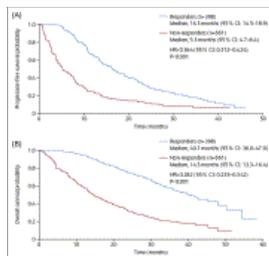

Fig. 2.
Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival in responders versus non-responders to sunitinib.

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Table 4. Progression-free and overall survival by treatment setting in responders and non-responders to sunitinib.

Population	Median time to progression/survival event, months (95% CI)		HR (95% CI)	P value
	Responders [n]	Non-responders [n]		
Progression-free survival				
All patients	16.3 (14.5–18.9) [398]	5.3 (4.7–6.4) [661]	0.364 (0.312–0.424)	<0.001
Treatment-naïve patients	16.3 (15.1–19.1) [301]	5.6 (4.8–6.9) [482]	0.394 (0.331–0.470)	<0.001
Cytokine-refractory patients	16.0 (12.4–19.2) [97]	4.8 (4.2–6.3) [179]	0.197 (0.138–0.282)	<0.001
Overall survival				
All patients	40.1 (36.0–47.9) [398]	14.5 (13.3–16.4) [661]	0.282 (0.233–0.342)	<0.001
Treatment-naïve patients	42.7 (35.5–NR) [301]	15.3 (13.4–17.5) [482]	0.304 (0.243–0.379)	<0.001
Cytokine-refractory patients	39.5 (33.1–47.9) [97]	13.1 (10.6–14.5) [179]	0.224 (0.154–0.328)	<0.001

CI, confidence interval; HR, hazard ratio; NR, not reached.

Using a Cox proportional regression analysis (data not shown), tumour response was an independent predictor of both PFS and OS ($P < 0.001$), independent of time on treatment, which itself was also predictive of PFS and OS ($P < 0.001$). A separate logistic regression analysis (data not shown) showed a trend for tumour response as a function of relative dose intensity but the association was not significant ($P = 0.0840$).

In the Cox proportional-hazards landmark analyses, response at ≤12 weeks was found to be independently predictive of both longer PFS and OS (both $P < 0.0001$; Supplementary Tables 1 and 2). (For purposes of the landmark analysis, if a patient had his/her first response after 12 weeks, then he/she was classified as a non-responder; therefore, late responders are not accounted for in this analysis.)

The proportion of patients who discontinued sunitinib treatment due to an adverse event was slightly less in responders compared with non-responders (15% versus 20%, respectively), a trend that was maintained regardless of treatment setting (data not shown).

Back to Article Outline

4. Discussion

Reflecting results from the six individual trials comprising the pooled database, OR was achieved in a robust 38% of the 1,059 sunitinib-treated patients with mRCC. Median TTR was 10.6 weeks (range 2.7–94.4 weeks), with 39% of patients experiencing a response after 12 weeks of therapy. Generally, efficacy outcomes were similar in early and late responders, including median

duration of response (52.0 versus 55.0 weeks) and median OS (37.8 versus 40.8 months), as were most baseline patient characteristics; however, median PFS was significantly shorter in early responders (13.8 versus 20.2 months) who had a higher frequency of baseline lung metastases, were younger and had a shorter interval since initial diagnosis. This apparent advantage for late responders was possibly the result of an implicit bias resulting from longer duration of therapy before progression.

As might have been expected, responders had significantly longer median PFS (16.3 versus 5.3 months) and OS (40.1 versus 14.5 months), as compared with non-responders, in which achievement of OR was predicted by favourable pretreatment prognostic factors. These included better ECOG performance status, favourable MSKCC risk status, higher rates of prior nephrectomy, fewer bone metastases and a longer interval since initial diagnosis, all of which have been identified in previous analyses of prognostic factors for survival in mRCC, including studies specifically for sunitinib [13], [14], [15]. In addition, tumour response was shown to be an independent predictor of survival to sunitinib, with response independent of time on treatment and relative dose intensity.

Based on median TTR (10.6 weeks) and the percentage of patients who achieved OR after 12 weeks of therapy (39%), a clinically important implication of this study is that it suggests physicians should allow patients sufficient time to obtain clinical benefit with sunitinib. Lack of early response should not be considered an indication of treatment failure and therapy should not be prematurely switched for reasons other than disease progression or unmanageable toxicity. Late responders had significantly longer median PFS and comparable (if not numerically longer) median OS. Therefore, if necessary for management of toxicities, dose modification, as opposed to interruption or discontinuation, should be considered in order to continue and optimise treatment with sunitinib.

These findings are consistent with data from a pharmacokinetic/pharmacodynamic meta-analysis of six sunitinib studies, including two in mRCC, which demonstrated that greater sunitinib exposure was associated with longer median OS [16], highlighting the importance of maintaining patients on the appropriate dose of sunitinib. Likewise, the pivotal phase III mRCC study demonstrated the potential survival benefit achievable to patients who stayed on the approved sunitinib 50 mg/day dose on Schedule 4/2 [8]. Furthermore, a randomised phase II study of the approved sunitinib regimen versus 37.5 mg continuous daily dosing in treatment-naïve patients with advanced RCC found numerically longer time to tumour progression with 50 mg/day on Schedule 4/2, leading the authors to conclude that it should remain the treatment goal [10]. However, retrospective analyses using data from both trials also indicate that efficacy can be maintained when dose reduction is associated with prolonged treatment duration [17].

Based on discontinuation rates due to adverse events (15% versus 16%), treatment tolerability appeared to be similar in early and late responders in the first-line setting, respectively; however, in the cytokine-refractory setting, early responders discontinued less frequently than late responders (8% versus 20%).

In addition to the usual limitations for a retrospective analysis, a potential limitation of the responders versus non-responders analysis is a presumed inherent bias favouring responders. Patients who eventually become responders must have lived long enough to be evaluated for a response and are therefore provided a guarantee time for survival. However, a valid and recommended statistical method for addressing such bias is to conduct a landmark analysis [18]. In the 12-week landmark analyses reported here, early response was independently predictive of both longer PFS and OS ($P < 0.0001$), thus addressing such concerns.

In summary, these analyses demonstrate the robust and durable response possible with sunitinib treatment in mRCC and the subsequent potential for prolonged survival predicted by response, regardless of its timing. These findings have important implications for clinicians regarding expectations of treatment with sunitinib in order to optimise clinical benefit for their patients.

Back to Article Outline

Role of the funding source

Back to Article Outline

Conflict of interest statement

Back to Article Outline

Acknowledgements

Back to Article Outline

Appendix A. Supplementary data

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Supplementary Tables. This document contains Supplementary Tables 1 and 2.

Back to Article Outline

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« Back

European Journal of Cancer