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ORIGINAL ARTICLE

Sunitinib rechallenge in advanced renal cell carcinoma: outcomes of a multicenter retrospective study

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Abstract

Purpose The aim of this multicenter study was to evaluate the clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) who received sunitinib retreatment.

Methods Clinical data from patients treated with sunitinib rechallenge in nine Spanish centers were retrospectively analyzed. All patients received first-line sunitinib until progression or intolerance, followed by one or more successive drugs and rechallenge with sunitinib thereafter.

Results Thirty-seven patients were included. At first-line treatment, objective response rate (ORR) was 69.4% and median progression-free survival (PFS) was 19.4 months. At rechallenge, ORR was 27.2% and 39.4% of patients obtained stabilization of disease. Median PFS was 6.2 months. Clinical benefit was obtained by 21 patients (75%) with > 6-month interval between sunitinib treatments and by 1 patient (20%) among those with ≤ 6-month interval ($P = 0.016$). Hemoglobin levels ≥ lower level of normal were associated with clinical benefit ($P = 0.019$) and with PFS ($P = 0.004$). Median overall survival from start of first-line sunitinib was 52.7 months. No new adverse events were observed at rechallenge.

Conclusions Sunitinib rechallenge is a feasible treatment option for selected patients with mRCC.

Keywords Renal cell carcinoma · Sunitinib · Rechallenge · Sequential therapy

Introduction

Worldwide incidence of renal cell carcinoma (RCC) is increasing by 2% annually. In Europe, more than 88,000 new cases per year are diagnosed [1]. Clear-cell RCC (ccRCC) accounts for 75% of all RCC. In these tumor types, the von Hippel–Lindau (VHL) gene is inactivated in more than 80% of cases, either by mutation or by methylation. Inactivation of the VHL gene leads to lack of ubiquitination of hypoxia-inducible factor-1α (HIF-1 α), a transcription factor that acts on many genes, such as vascular endothelial growth factor (VEGF), resulting in aberrant angiogenesis [2–4], which is one of the hallmarks of cancer [5]. The mammalian target of rapamycin (mTOR) pathway is also altered in ccRCC,

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leading to tumor growth and angiogenesis [6–8]. Tyrosine kinase inhibitors (TKI) of the vascular endothelial growth factor (VEGF) pathway, and mTOR inhibitors (mTORI) have been the backbone of the treatment of metastatic renal cell carcinoma (mRCC). Until recently, the VEGF receptor TKI sunitinib and pazopanib have been the standard first-line treatments for favorable and intermediate-risk patients, while the mTOR inhibitor temsirolimus was indicated for poor-risk patients [9]. Despite the clear survival benefit obtained from targeted drugs, some tumors are primarily refractory to VEGF pathway inhibition, resulting in poor prognosis [10]. Half of patients initially responders to sunitinib progress within 9–11 months from the start of treatment [11, 12]. Several mechanisms are involved in this adaptive resistance, including activation of non-VEGF-depending angiogenic pathways and overexpression of cMET receptor, which promotes cell proliferation, survival and invasiveness [13]. In recent years, interaction of sunitinib with tumor immune microenvironment has aroused growing interest. Treatment of patients with RCC with sunitinib mediates a decrease in circulating myeloid-derived suppressor cells (MDSCs) [14] and regulatory T cells (Tregs), and a decrease of intratumoral Tregs, without association with tumor response [15]. On the other hand, tumors from patients treated with VEGFI showed higher infiltration of Tregs and enhanced expression of programmed death-ligand 1 (PD-L1), and both immunosuppressive features were inversely correlated with survival [16]. Interaction between angiogenesis and immune response has led to the combination of immune checkpoint inhibitors and VEGF/VEGFR-targeted drugs, a strategy that shows promising results [17]. In 2018, the phase III CheckMate 214 trial compared the combination of nivolumab and ipilimumab (which blocks the cytotoxic T-lymphocyte antigen 4, CTLA-4) with sunitinib in the first-line setting. The combination arm was clearly superior to sunitinib in patients in the intermediate- or poor-risk groups; nevertheless, sunitinib remained the best option for low-risk patients [18]. Moreover, sunitinib is still a recommended drug for papillary and other varieties of non-clear RCC [19, 20]. These recommendations have been included in the latest RCC guidelines [21]. Therefore, further investigations on the role of sunitinib in different treatment settings are still of interest.

Since the onset of targeted therapies, many prospective and observational studies have addressed the problem of optimal treatment sequence [22]. In this context, several observational studies on rechallenge with sunitinib as third treatment arm and beyond have been reported [23–26] (Table 1). To date, the largest series of patients rechallenged with sunitinib is that of a multicenter, observational, retrospective and prospective study (RESUME trial) [26]. Fifty-two patients who received first-line sunitinib followed by at least one alternative therapy before sunitinib re-exposure were included. Only one patient was classified as poor risk of the MSKCC prognostic score [27]. Median time between sunitinib treatments was 14.6 months. Median PFS was 18.4 months on first-line sunitinib and 7.9 months on sunitinib rechallenge. Duration of first-line treatment was associated with prolonged PFS at rechallenge. Median overall survival (OS) was 55.9 months. Asthenia was clearly more frequent at rechallenge than was at first-line treatment (22% vs 7%, respectively), probably as a reflection of more advanced disease.

Table 1 Sunitinib rechallenge

Author, year (Ref.)	*N*	Patient characteristics at first-line treatment	Initial sunitinib PFS (months)	Interval initial treatment—rechallenge (months)	Rechallenge PFS
Zama et al., 2010 [17]	23	Median age: 59 years Clear cell: 100% Karnofsky PS: 90–100 (22%) 80–90 (78%)	21.0	6.7 (1.3–22.0)	7.2
Grünwald et al., 2011 [18]	13	Median age: 58 years Clear cell: 92% ECOG PS: 0 (69%) 1 (31%)	21.0	13	6.9
Oudard et al., 2016 [16]	50	Median age: 59.3 years Clear cell: 98% ECOG PS: 0 (81%) 1 (14%) > 1 (5%)	18.4	14.6	7.9
Nagyiványi et al., 2019 [19]	21	Median age: 56 years Clear cell: 90%	22	14 (3–53)	14

Data from retrospective studies

N number of patients, *PFS* progression-free survival

Here we report the results obtained in a multicenter series of 37 patients rechallenged with sunitinib, including efficacy and toxicity data, as well as factors influencing clinical outcomes on rechallenge. To our knowledge, this work includes the largest number of patients after the RESUME study [26].

Materials and methods

This retrospective study was conducted in nine Spanish centers. Eligibility criteria included patients with confirmed metastatic RCC of any histology. Additional criteria were treatment with first-line sunitinib until progression or intolerance, followed by one or more subsequent drugs, and then treated with sunitinib rechallenge. Patient and initial tumor characteristics, interval between sunitinib treatments, intervening therapies and OS were recorded. Analytical data with potential prognostic value, tumor response and PFS were collected for both initial and rechallenge sunitinib treatments. The study was approved by the institutional ethics boards of the participating institutions.

Statistical analysis

A descriptive analysis of all variables was performed. Qualitative data were analyzed by means of absolute and relative frequencies. Quantitative variables were summarized as means, standard deviations and confidence intervals, or by medians and ranges for data without a normal distribution. Pearson's Chi-square test or Fisher's exact test was used to compare qualitative samples; Student's *t* test, ANOVA or their non-parametric equivalents (*U* Mann–Whitney, *H* Kruskal–Wallis) were used for comparisons of quantitative samples. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), v1.1 [28]. Progression-free survival (defined as the time between start of each sunitinib therapy and disease progression or death) and OS (calculated as the time between the start of initial sunitinib treatment and death, and from diagnosis and death) were estimated by Kaplan–Meyer method. Log rank test was used to compare survival curves according to qualitative variables.

Results

Initial sunitinib

Thirty-seven patients who started sunitinib rechallenge between April 2011 and July 2015 were included. Table 2 summarizes patient characteristics and outcomes relating to initial sunitinib treatment. Most patients were male; median age at first sunitinib treatment was 56 years, and all of them had prior nephrectomy. All patients but one had clear cell histology. Most patients had less than three metastases. No complete responses were observed with initial sunitinib; partial response rate was 69.4% and median PFS was 19.37 months (95% CI 8.30–30.43; Fig. 1a). Disease progression was the most frequent reason (78%) for sunitinib discontinuation.

Sunitinib rechallenge

Table 3 summarizes the patient outcomes on sunitinib rechallenge. The median time between discontinuation of initial sunitinib and start of rechallenge was 14 months. Sunitinib rechallenge was given as third-, fourth-, and fifth-line therapy to 43%, 43% and 14% of patients, respectively. During the intervening period, 19% of patients received an mTORI, 22% a TKI, and 59% were treated with both types of drugs. Nine patients (27.2%) achieved a partial response upon sunitinib rechallenge (including one patient with stable disease as best response with initial sunitinib), and 13 (39.4%) had stable disease; clinical benefit, defined as the sum of objective response and stable disease, was, therefore, obtained by 22 patients (66.7%). Objective response and clinical benefit rates were significantly better in the initial sunitinib treatment than in the rechallenge setting ($P = 0.008$). Median PFS was 6.20 months (95% CI 3.71–8.69; Table 3 and Fig. 1b). Median OS from diagnosis was 78.5 months (95% CI 58.7–98.3), and median OS from start of initial sunitinib was 52.97 months (95% CI 38.07–67.86; Fig. 1c).

Factors associated with treatment response

Fuhrman grade (≥ 3 vs < 3), hemoglobin levels [$\geq$ lower level of normal (LLN) vs $<$ LLN], neutrophil to lymphocyte ratio (NLR) (≥ 3 vs < 3), and platelet count ($\geq 300{,}000/\mu L$ vs $< 300{,}000/\mu L$) were analyzed as potential prognostic factors, either in the initial treatment or in the rechallenge period. Corrected calcium and lactate dehydrogenase levels were discarded because all patients with available data had normal levels of both parameters. The interval between discontinuation of initial sunitinib and start of rechallenge (≤ 6 months vs > 6 months) was also analyzed as a potential predictor of rechallenge efficacy. Twenty-eight patients with analytical data were evaluable for response. In the rechallenge period, 11 of the 12 patients (91.7%) with hemoglobin $\geq$ LLN achieved clinical benefit, compared to 8 out of 16 patients (50%) with hemoglobin $<$ LLN ($P = 0.019$); an objective response was achieved by 8 and 4 patients, respectively, but this difference did not reach statistical significance. Clinical benefit and ORR obtained by patients with NLR < 3 vs NLR ≥ 3 were not significantly different either, although 5 out of 14 patients with NLR < 3 had

Table 2 Baseline patient characteristics and outcome at time of first-line sunitinib therapy ($N=37$)

Gender	
Male	29
Female	8
Median age (range)	56 (34–76)
Median time from diagnosis to first-line sunitinib (range), months	17.5 (0.3–169)
Prior nephrectomy, *N* (%)	37 (100)
Clear cell histology, *N* (%)	36 (97.2)
Fuhrman grade, *N* (%)	
I	1 (3.0)[a]
II	13 (39.4)[a]
III	15 (45.5)[a]
IV	4 (12.1)[a]
NA	4 (10.8)
Metastatic sites	
Lymph nodes	14
Lung	24
Bone	5
Liver	5
Adrenal gland	3
Pancreas	3
Other[b]	3
Number of metastatic sites, *N* (%)	
1–2	23 (62.1)
> 2	14 (37.8)
Median duration of treatment, median (interval), months	18.25 (8.2–32.4)
Reason for discontinuation, *N* (%)	
Disease progression	29 (78.4)
Toxicity	3 (8.1)
Other	5 (13.5)
Median time from start of treatment to best response (interval), months	5.8 (3.8–9.4)
Best response, *N* (%)	
Complete response	0 (0.0)[a]
Partial response	25 (69.4)[a]
Stable disease	9 (25.0)[a]
Disease progression	2 (5.5%)[a]
NA	1 (2.7)
Median PFS (95% CI), months	19.4 (8.3–30.4)

NA not available

[a]Percentage based on the number of patients with available data

[b]Thyroid gland, bladder and gluteus (one each)

objective response, compared to 1 of the 14 patients with NLR ≥ 3. Six patients (30%) with platelet count < 300,000/μL had partial response vs 0 patients with platelet count ≥ 300,000/μL ($P=0.081$). The interval between sunitinib treatments was ≤ 6 months for 5 patients, and > 6 months for 28 patients. Twenty-one patients (75%) with a > 6-month interval between sunitinib treatments achieved clinical benefit, compared to 1 patient (20%) among those who started the rechallenge within 6 months from their initial treatment ($P=0.016$); however, the ORRs did not reach a statistically significant difference (9 patients, 32.1%, vs 0 patients, respectively; $P=0.137$). Only Hb levels (≥ LLN vs < LLN) had a significant influence on PFS (median PFS, 11.7 months (95% CI 0.0–1.1) vs 3.9 months (95% CI 1.1–6.7), respectively, $P=0.004$). None of these factors showed a statistically significant influence on response or PFS in the initial treatment setting. No linear correlation between PFS obtained with initial sunitinib and rechallenge was observed ($P=0.8$); five patients (13.5%) had a longer PFS with rechallenge than with initial sunitinib (Fig. 1c). A

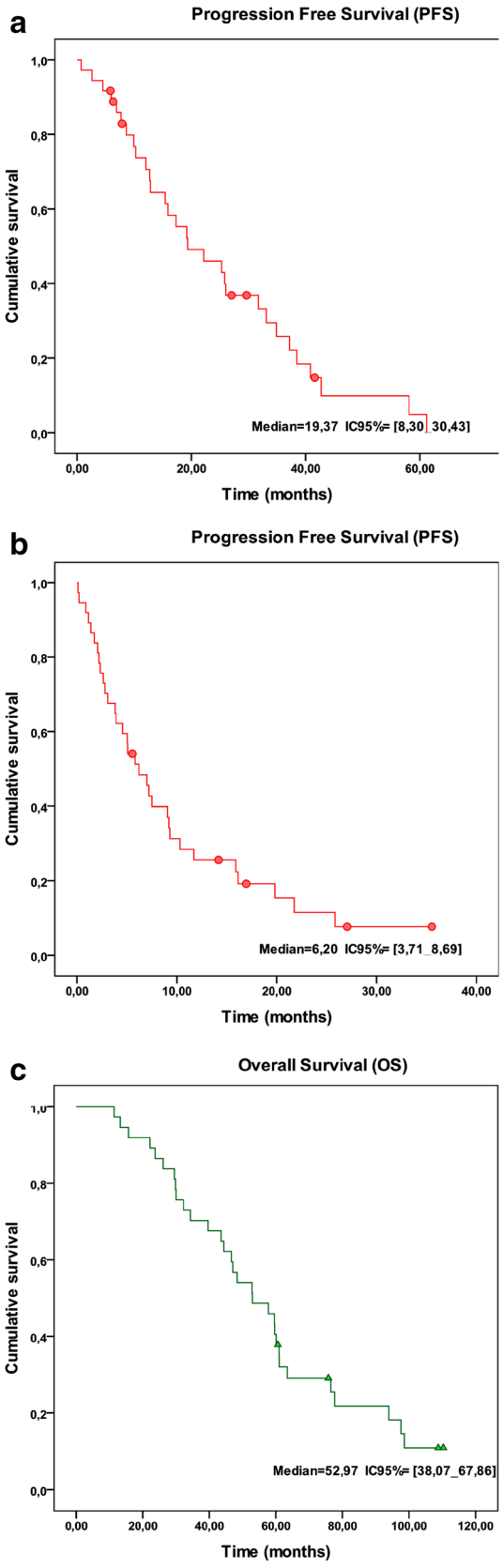

Fig. 1 Progression-free survival with **a** initial sunitinib and **b** sunitinib rechallenge; **c** overall survival from initial sunitinib

borderline association was found between median OS from initial sunitinib and pretreatment platelet count (≥ 300,000/μL vs < 300,000/μL): 60.1 months (95% CI 40.0–80.1) vs 32.2 months (95% CI 25.2–39.2), $P = 0.051$.

Table 3 summarizes the characteristics studied and their association with outcome in the rechallenge period.

Safety

Toxicities registered on initial sunitinib and rechallenge are shown in Table 4. Thirty-three patients in the initial sunitinib setting and 34 patients in the rechallenge period had available toxicity data. Fatigue, palmo-plantar erythrodysesthesia (PPED), mucositis, anemia and hypertension were the most commonly observed adverse events in both treatment periods and, except for anemia, were somewhat more frequent in the rechallenge setting (Fig. 2).

Discussion

Clear cell RCC is one of the malignant tumors in which treatment options have expanded and evolved more rapidly. After progression to initial treatments, second- and third-line options, that include alternative TKI, mTORI or immunotherapy, have been included in current guidelines [21]. Nevertheless, beyond second-line therapies, recommendations are necessarily ground on extrapolations and post hoc subgroup analyses rather than on high-quality evidence.

The present study suggests that sunitinib rechallenge is a reasonable option after second-line and successive treatments. Progression-free survival was over 6 months, although 57% of patients received sunitinib rechallenge as at least fourth-line therapy. Previous studies of sunitinib rechallenge have yielded median PFS in the range of 6.8–7.9 months [23–26]; of them, only the study by Oudard et al. [26] provides median OS of patients (55.9 months, not far from the 52.97-month median OS obtained in our study).

Regarding factors associated with rechallenge outcomes, hemoglobin levels (≥ LLN vs < LLN) showed a significant association with clinical benefit and with PFS, while NLR (≥ 3 vs < 3), and platelet count (≥ 300,000/μL vs < 300,000/μL) showed a trend to associate with objective response. On the other hand, the interval between sunitinib treatments (≤ 6 months vs > 6 months) was associated with clinical benefit and showed a trend to associate with objective response. In contrast with data reported by Zama et al. [23], sunitinib treatment interval did not impact on PFS. Of note, PFS of some patients was longer with rechallenge than with initial sunitinib, underlying the importance of tumor changes along their evolution (Table 5).

Toxicity profile on sunitinib rechallenge was not worse than that observed with initial sunitinib, with only two new

Table 3 Patient characteristics and outcome on sunitinib rechallenge ($N = 37$)

Median time from end of 1st sunitinib to rechallenge (range), months	14.0 (0.9–74.7)
Intervening systemic treatments between 1st sunitinib and rechallenge[a]	
Everolimus	26
Sorafenib	18
Pazopanib	11
Axitinib	5
Temsirolimus	2
Bevacizumab	1
Clinical trial	1
Median duration of treatment (range), months	6.2 (2.8–14.2)
Reason for discontinuation, *N* (%)	
Disease progression	30 (81.1)
Toxicity	4 (10.8)
Other	1 (2.7)
Median time from start of rechallenge to best response (range), months	3.0 (1.4–5.5)
Best response	
Complete response, *N* (%)	0 (0.0)
Partial response, *N* (%)	9 (27.2%)[b]
Stable disease, *N* (%)	13 (39.4%)[b]
Disease progression, *N* (%)	11 (33.3%)[b]
Clinical benefit[c], *N* (%)	22 (66.7)[b]
NA	4 (10.8)
Median PFS (95% CI), months	6.2 (3.7–8.7)
Systemic treatments received after sunitinib rechallenge	
TKI	5
mTORI	2
TKI + mTORI	4
INF + bevacizumab	1

NA not available, *TKI* tyrosine kinase inhibitor, *mTORI* mammalian target of rapamycin inhibitor, *INF* interferon α-2a

[a]All patients received one or more treatments

[b]Percentage based on the number of patients with available data

[c]Sum of patients with complete response, partial response and stable disease

adverse events (renal toxicity and hyponatremia, one each). Toxicities that could be expected to be more frequent in the rechallenge treatment had similar or even less incidence than in the initial sunitinib period, as with PPDE, mucositis and fatigue, among others.

The emergence of new options in the second-line setting raises the question of their potential influence in successive treatments, including sunitinib rechallenge. As mentioned above, sunitinib treatment leads to a decrease in circulating MDSCs and Tregs [14, 15]. On the other hand, RCC specimens from patients treated with sunitinib and other VEGF-targeted therapies showed an enhanced expression of PD-L1 and Treg infiltration [16]. In turn, expression of PD-L1has been associated with poor VEGF-TKI responsiveness and shorter PFS and OS in patients with metastatic RCC [29]. Cabozantinib, one of the new players in the treatment of RCC that targets VEGF receptors, MET and AXL, can reverse resistance to sunitinib in preclinical models by suppression of chronic sunitinib-induced AKT, ERK and EMT signaling activation, cell migration and invasion [30]. The TAM receptor kinase AXL has been implicated in PD-L1 expression [31]; thus, TAM receptor inhibitors such as cabozantinib might also sensitize tumors to further VEGFR-TKI treatments, including sunitinib, through down-regulation of PD-L1 expression. With regard to the influence of nivolumab on the efficacy of successive therapies, a retrospective study showed that treatment with VEGFR-TKIs has clinical activity and can be safely done after PD-1 inhibition [32]. To what extent these data may have an impact on the efficacy of retreatment with VEGFR-TKIs remains to be elucidated.

Our study has several limitations. Data have been obtained by retrospective review of the medical records of non-monitored patients from nine institutions; therefore,

Table 4 Factors influencing patient outcomes on sunitinib rechallenge

Factor	Clinical benefit[a]			Objective response[b]			PFS		
	Number of patients evaluated ($N=37$)	Number of patients with CB (%)	*P*	Number of patients evaluated ($N=37$)	Number of patients with OR (%)	*P*	Number of patients evaluated ($N=37$)	Median (95% CI)	*P*
Hb	28			28			31		
≥LLN	12 (69.7)	11 (91.7)	0.019	12 (69.7)	8 (66.7)	0.184	12 (38.7)	11.7 (0.0–1.1)	0.004
<LLN	16 (30.3)	8 (50.0)[c]		16 (30.3)	4 (33.3)		19 (61.2)	3.9 (1.1–6.7)	
NLR	28			28			31		
<3	14 (50)	11 (78.6)	0.225	14 (50)	5 (35.7)	0.065	15 (48.3)	6.2 (1.1–11.2)	0.582
≥3	14 (50)	8 (57.1)		14 (50)	1 (7.1)		16 (51.6)	3.9 (0.0–9.7)	
Platelets	28			28			31		
$<3\times10^5$	20 (71.4)	13 (65)	0.609	20 (71.4)	6 (30)	0.081	21 (67.7)	7.0 (5.0–8.9)	0.326
$\geq3\times10^5$	8 (28.5)	6 (75)		8 (28.5)	0 (0.0)		10 (32.2)	3.8 (1.8–5.7)	
Interval (m)	33								
>6	28 (84.8)	21 (75)	0.016	28 (84.8)	9 (32.1)	0.137	28 (84.8)	7 (4.7–9.2)	0.897
≤6	5 (15.1)	1 (20)		5 (15.1)	0 (0.0)		5 (15.1)	7.0 (2.0–3.3)	

CB clinical benefit, *OR* objective response, *PFS* progression-free survival, *Hb* hemoglobin, *LLN* lower limit of normal, *NLR* neutrophil to lymphocyte ratio

[a]Sum of patients with complete response, partial response and stable disease

[b]Sum of patients with complete response and partial response

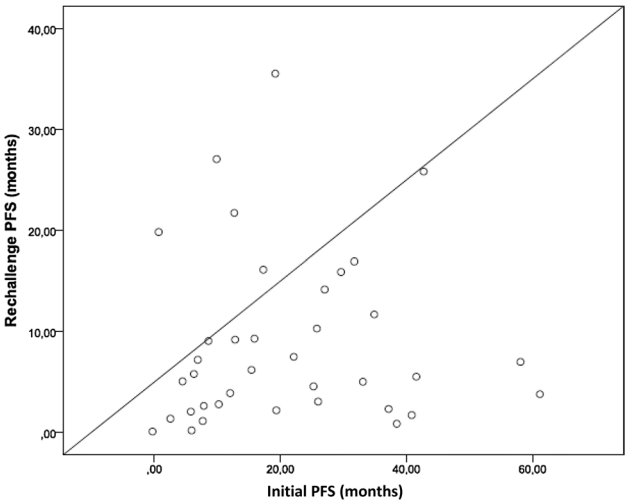

Fig. 2 Correlation between progression-free survival with initial sunitinib and with sunitinib rechallenge

some data have not been available for all patients. Notably, information on ECOG or Karnofsky performance status, key parameters for building established prognostic models, lacked sufficient quality to be included. Furthermore, the small number of patients led to biases and lack of significancy of some calculations that otherwise would probably provide more consistent conclusions.

Despite these limitations, the present study supports the conclusions drawn from similar previous publications. In

Table 5 Toxicities on initial sunitinib treatment and sunitinib rechallenge

	Initial sunitinib ($N=33$)	Sunitinib rechallenge ($N=34$)
Toxicity	*N* (%) [grade > 2]	*N* (%) [grade > 2]
PPDE	9 (27) [3]	5 (15)
Cutaneous	4 (12) [1]	2 (6)
Mucositis	9 (27)	5 (15) [1]
Edema	1 (3)	1 (3) [1]
Fatigue	19 (58) [1]	14 (41)
Anorexy	1 (3)	2 (6)
Dysgeusia	2 (6)	1 (3)
Anemia	5 (15)	6 (18) [1]
Neutropenia	3 (9) [1]	2 (6)
Thrombocytopenia	1 (3)	3 (9)
Cardiac	1 (3) [1]	1 (3)
Hypothyroidism	3 (9)	3 (9) [1]
Hypertension	9 (27) [1]	6 (18)
Diarrhea	5 (15)	2 (6)
Hepatic	2 (6)	2 (6)
Bilirubin elevation	1 (3)	1 (3)
Renal	–	1 (3)
Hyponatremia	–	1 (3)

PPDE palmo-plantar dysesthesic erythema

summary, sunitinib rechallenge is a safe and reasonable option after progression to one or more intervening drugs, particularly when access to other treatment modalities is restricted.

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Compliance with ethical standards

Conflict of interest Dr. Gaspar Reynés, Dr. Puente and Dr Climent have received travel support and honoraria from Pfizer. The other authors declare to have no conflicts of interest.

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