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Original article

Clinical outcome of patients who reduced sunitinib or pazopanib during first-line treatment for advanced kidney cancer

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Abstract

Objectives: To investigate the different outcomes in patients with metastatic renal cell carcinoma (mRCC) who receive a reduced first-line dose of sunitinib or pazopanib compared to those who continue at the standard dose.

Patients and methods: All the patients treated in 11 oncological centers in Italy for mRCC who started first-line treatment with sunitinib or pazopanib at the standard dose. Descriptive statistical tests were used to highlight differences among groups. Survival was estimated by the Kaplan-Meier method and compared across the groups using log-rank tests, the Cox proportional hazards model adjusted for statistically significant variables was also done.

Results: A total of 591 patients were included in the study. Of these, 45.7% received a reduced dose of sunitinib or pazopanib after a median treatment time of 3.6 months at the standard dose. The median overall survival in the patients who continued to receive the standard dose was 24.0 months compared to 49.4 months for those who received a reduced dose (hazard ratio = 1.80; 95% CI: 1.42–2.29; $P < 0.001$).

Only 45% of the patients received second-line therapy: 42.5% had an mTOR and 54.1% a tyrosine kinase inhibitor. Second-line overall survival was 19.8 and 11.8 months, respectively, in the patients who received, or did not, a reduced dose during first-line therapy ($P = 0.007$).

Conclusions: Toxicity-related dose reduction is a common event in mRCC patients who have started first-line therapy with either sunitinib or pazopanib. This is positively related to the outcomes of both first- and second-line therapy.

Keywords: mRCC; Dose reduction; Toxicity; Survival; Sunitinib; Pazopanib; First-line; Second-line

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1. Introduction

In recent years, many drugs targeting the vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGFR) axis have been approved for the treatment of metastatic renal cell carcinoma (mRCC) based on advantages in clinical outcomes demonstrated in large phase III clinical trials. Among these drugs, sunitinib and pazopanib are both considered to be standard first-line treatment and were recently compared in a noninferiority phase III trial that reported similar outcomes with a different toxicity profile [1,2]. Despite an increased understanding of drug-related toxicity profiles and the improved expertise of the clinicians involved in the management of mRCC patients, both drugs are characterized by a variety of adverse events that lead to dose interruptions or reductions in more than 40% of cases [1].

In general, treatment-related toxicity negatively affects a patient's quality of life, although suboptimal tolerability leading to dose reduction has long been considered to undermine the benefits of therapy. To improve patient outcomes, early identification, prevention, and the treatment of toxicities are crucial for maximizing the efficacy of therapy. Recently, a model has also been proposed for predicting toxicity-related treatment discontinuation in patients with mRCC receiving VEGFR inhibitors. In this model, age, the glomerular filtration rate, the number of metastatic sites, and baseline sodium levels were found to be independent risk factors for toxicity-related treatment discontinuation [3].

Despite this, the outcomes of patients who receive a reduced dose due to treatment-related adverse events have been investigated less. Herein, we aim to describe the effects of dose reductions as a consequence of treatment-related toxicity on the outcomes of patients with mRCC treated with standard first-line sunitinib or pazopanib.

2. Materials and methods

2.1. Patients

Patients with mRCC treated in 11 oncological centers in Italy with first-line sunitinib or pazopanib were included in the study. The patients were required to have a histological diagnosis of clear cell RCC and to have started first-line treatment at the standard doses (i.e., sunitinib = 50 mg daily with a 4/2 schedule; pazopanib = 800 mg daily continuously). Adequate information about the baseline Eastern Cooperative Oncology Group performance status, the extent of the disease, and the biochemical parameters (i.e., hemoglobin, platelets, neutrophils, and serum calcium) was also required. The patients should also have been given information about dose reductions, as well as the date and level of dose they were receiving and the main reason for any changes. Toxicity was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [4]. A prognostic group at baseline was evaluated for each patient using the International mRCC Database Consortium (IMDC) criteria [5]. Data on the type (mTOR vs. tyrosine kinase [TK] inhibitors) and length of second-line therapy were also collected.

The patients were divided into 2 groups based on whether they had experienced a dose reduction or not during first-line treatment. Baseline characteristics and outcomes were analyzed separately. The patients who received reduced-dose treatment were also classified based on the level of dose: first (i.e., sunitinib = 37.5 mg; pazopanib = 600 mg) or second level (i.e., sunitinib = 25 mg; pazopanib = 400 mg).

2.2. Statistics

Baseline values were expressed as the median and interquartile range. The baseline was defined as the start date of treatment with sunitinib or pazopanib. Progression-free survival (PFS) was evaluated from the start of first- or second-line treatment to the progression of the disease or death. The patients were assessed for progression according to the Agenzia Italiana del Farmaco (AIFA) Italian guidelines every 12 weeks, with progression evaluated by RECIST v. 1.0. Overall survival (OS) was evaluated from the baseline (OS1) or from the start of second-line therapy (OS2) to death. All the survival rates were estimated using the Kaplan-Meier method and compared across groups using the log-rank test. Survival rates were also adjusted for the IMDC prognostic classification. A landmark analysis was conducted to estimate PFS to avoid both selection bias and the inclusion of patients with negative prognostic features and, consequently, a shorter PFS (<4 mo).

A chi square or *t*-test was used to compare groups when appropriate. The association of dose reduction as a continuous variable with OS or PFS was evaluated using the Cox proportional hazards model, and the values were adjusted for the IMDC criteria, age, sex, and whether or not a nephrectomy had been performed. All the variables were considered to be significant at the level of $P < 0.05$. The PASW software (Predictive Analytics SoftWare; v 21; IBM SPSS) was used for the analysis. The approval of the Ethics Committee was required and obtained for this study.

3. Results

A total of 591 patients, treated from 2006 to 2016, were included in the analysis. Sunitinib was the first-line treatment in 76.5% of cases and pazopanib in the remaining 23.5%. The baseline characteristics for the entire population are reported in Table 1. At the date of the analysis, after a median follow-up of 36 months, 421 patients had experienced disease progression and 281 had died. In the overall group, the median OS was 33.8 months (95% CI: 29.0–38.6) and the median PFS was 13.4 months (95% CI: 11.8–15.1).

Table 1
Baseline characteristics of the patients

Characteristics	Patients	First-line dose reduction		χ^2
	$N = 591$	No $N = 321$	Yes $N = 270$	P value
Median age	63.2 (IQR: 55.4–70.9)	61.4 (IQR: 52.6–69.5)	65.1 (IQR: 58.4–72.4)	<0.001[a]
Male sex	70.7%	74.1	66.6	0.09
Nephrectomy	87.3%	83.5	91.9	0.002
Metastatic at diagnosis	43.1%	47.7	37.7	0.016
Performance status				
ECOG = 0	70.9%	68.8	73.3	0.2
ECOG = 1	25.2%	26.2	24.1	
ECOG = 2	3.9%	5.0	2.6	
Hb < LLN	35.5%	36.8	34.1	0.5
Corrected Ca > ULN	6.1%	7.5	6.3	0.6
PLT > ULN	8.8%	11.2	5.9	0.024
Neu > ULN	12.0%	14.0	9.6	0.1
Sites of disease				
Lung	61.8%	62.3	61.1	0.8
Nodes	48.4%	47.0	50.0	0.5
Bone	28.9%	32.4	24.8	0.04
Liver	17.6%	20.6	14.1	0.04
Local	14.5%	12.8	15.9	0.3
Pancreas	11.0%	8.4	14.1	0.03
Brain	7.3%	8.7	5.5	0.1
IMDC prognostic group				
Good	28.6%	24.9	33.0	0.003
Intermediate	58.2%	57.9	58.5	
Poor	13.2%	17.1	8.5	
Type of therapy				
Sunitinib	76.5%	77.3	75.6	0.6
Pazopanib	23.5%	22.7	24.4	

Ca = calcium; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; IMDC = International MRCC Database Consortium; IQR = interquartile range; LLN = low limit of normal; Neu = neutrophils; PLT = platelets; ULN = upper limit of normal.
[a] t Test.

A total of 270 patients (45.7%) received a reduced dose after a median period of 3.6 months on the standard dose (95% CI: 2.9–4.2). The median number of cycles received before dose reduction was 3 for both drugs (Fig. 1). In the patients treated with sunitinib, the dose was reduced to 37.5 mg and 25 mg daily for 4weeks in every 6 in 189 (44.5%) and 15 (3.3%) cases, respectively. In the patients treated with pazopanib, the dose was reduced to 600 mg and 400 mg daily in 46 (33.1%) and 20 (14.4%) cases, respectively.

Differences in the baseline characteristics between the patients who did or did not receive a reduced treatment dose are reported in Table 1. Those who required a dose reduction were more commonly older, had more often undergone a nephrectomy (91.9% vs. 83.5%), less frequently had metastases at diagnosis (37.7% vs. 47.7%), and more often had favorable prognostic features based on the IMDC classification (Table 1).

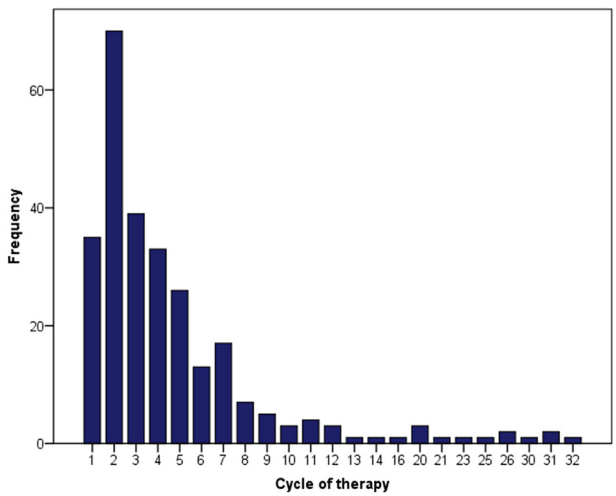

Fig. 1. Number of patients and cycle of dose reduction.

Table 2
Main reasons for dose reduction in 204 patients treated with sunitinib

Toxicity	All		G2		G3		G4	
	N	%	*N*	%	*N*	%	*N*	%
Asthenia	33	16.2	16	7.8	17	8.3	–	–
HF syndrome	34	16.7	13	6.4	21	10.3	–	–
Diarrhea	17	8.3	6	2.9	11	5.4	–	–
PLT decrease	24	11.8	4	2.0	20	9.8	–	–
Mucositis	20	9.8	7	3.4	13	6.4	–	–
Hypertension	11	5.4	4	2.0	7	3.4	–	–
Low WBC/neu.	9	4.4	–	–	9	4.4	–	–
Hepatic toxicity	1	0.5	1	0.5	–	–	–	–
Anemia	8	3.9	6	2.9	2	1	–	–
Cardiac toxicity	5	2.5	1	0.5	4	2	–	–
Creatinine increase	5	2.5	5	2.5	–	–	–	–
Nausea	3	1.5	2	1	1	0.5	–	–
Dysgeusia	–	–	–	–	–	–	–	–
Anorexia	2	1	1	0.5	1	0.5	–	–
Other causes	31	15.2	12	5.9	17	8.3	2	1

G = grade; HF = hand-foot; neu. = neutrophils; *N* = number; PLT = platelets; WBC = white blood cells.

The main reasons for the dose reductions in the overall population were asthenia (16.3%), hand-foot syndrome (13.3%), diarrhea (13.0%), and falls in platelet numbers (10.4%). Other reasons are reported separately for the patients treated with sunitinib (Table 2) or pazopanib (Table 3).

3.1. Outcomes of first-line treatment

The unadjusted median PFS of the patients who continued at the standard treatment dose was 9.2 months (95% CI: 7.0–11.3) compared to 18.1 months (95% CI: 15.6–20.6) for those whose dose was reduced (hazard ratio [HR] = 1.74; 95% CI: 1.43–2.12; $P < 0.001$). This difference was confirmed in the sunitinib population (7.0 vs. 18.1 mo; $P < 0.001$) and in the patients who had undergone a nephrectomy (11.1 vs. 18.6; $P < 0.001$). Once again, when the effect of dose reduction on PFS was adjusted for IMDC class, age, sex, and nephrectomy at baseline, it remained significant (HR = 0.60; 95% CI: 0.47–0.66; $P < 0.001$) (Fig. 2A, Supplementary Tables 1 and 3).

Table 3
Main reasons for dose reduction in 66 patients treated with pazopanib

Toxicity	All		G2		G3		G4	
	N	%	*N*	%	*N*	%	*N*	%
Asthenia	11	16.7	3	4.5	8	12.1	–	–
HF syndrome	2	3.0	–	–	2	3.0	–	–
Diarrhea	18	27.3	12	18.2	6	9.1	–	–
PLT decrease	3	4.5	1	1.5	2	3.0	–	–
Mucositis	2	3.0	2	3.0	–	–	–	–
Hypertension	3	4.5	–	–	3	4.5	–	–
Low WBC/neu.	2	3.0	1	1.5	1	1.5	–	–
Hepatic toxicity	8	12.1	2	3.0	6	9.1	–	–
Anemia	–	–	–	–	–	–	–	–
Cardiac toxicity	2	3.0	1	1.5	1	1.5	–	–
Creatinine increase	1	1.5	–	–	1	1.5	–	–
Nausea	1	1.5	–	–	1	1.5	–	–
Disgeusia	4	6.1	–	–	4	6.1	–	–
Anorexia	2	3.0	2	3.0		–	–	–
Other causes	7	10.6	5	7.6	2	3.0	–	–

G = grade; HF = hand-foot; neu. = neutrophils; *N* = number; PLT = platelets; WBC = white blood cells.

The unadjusted median OS of the patients who continued at the standard dose was 24.0 months (95% CI: 18.1–29.4) compared to 49.4 months (95% CI: 40.0–58.9) for those whose dose was reduced (HR = 0.60; 95% CI: 0.47–0.76; $P < 0.001$). This difference was confirmed in the sunitinib population (20.7 vs. 49.3 mo, $P < 0.001$) and in the patients who had undergone a nephrectomy (30.1 vs. 53.1, $P < 0.001$). When the effect of dose reduction on OS was adjusted for the IMDC class, age, sex, and nephrectomy at baseline, it remained significant (HR = 0.60; 95% CI: 0.49–0.73; $P < 0.001$) (Fig. 2B, Supplementary Tables 2 and 4). Further dose reductions to the second level were found to be related to a longer OS but not to a longer PFS (Supplementary Table 5).

This landmark analysis, which excluded 131 patients who did not receive at least 4 months of therapy, confirmed better outcomes with respect to both OS (HR = 0.69; 95% CI: 0.52–0.92; $P = 0.013$) and PFS (HR = 0.76; 95% CI: 0.61–0.95; $P = 0.016$) for those who received a reduced dose, even if the results were adjusted for the IMDC prognostic group.

3.2. Outcomes of second-line treatment

Among the 591 evaluable patients, only 266 (45%) received second-line therapy. This consisted of TK inhibitors in 113 cases (42.5%) and mTOR inhibitors in the remaining 144 (54.1%). The most frequent second-line treatments used were everolimus (53.3%), axitinib (21.4%), and sorafenib (16.2%). The unadjusted median second-line PFS of the patients who did not receive a reduced first-line dose was 3.7 months (95% CI: 3.0–4.4) compared to 5.7 months (95% CI: 4.4–7.1) for those who did ($P = 0.006$). The unadjusted median OS from the start of second-line therapy for the patients who did not receive a reduced first-line dose was 11.8 months (95% CI: 9.4–14.3) compared to 19.8 months (95% CI: 17.1–22.6) for those who did ($P = 0.007$).

In the patients treated with an mTOR inhibitor, 84 did not receive a reduced first-line dose and 60 had experienced a previous dose reduction. The median PFS was 3.1 months (95% CI: 2.4–3.8) for the first group and 4.6 months (95% CI: 2.5–6.6) for the second ($P = 0.007$) (Fig. 3A). The median OS was 11.4 months (95% CI: 8.8–14.0) for the first group and 19.6 months (95% CI: 14.9–24.3) for the second ($P = 0.016$) (Fig. 3B).

In the patients treated with a TK inhibitor, 54 did not receive a reduced first-line dose, whereas 59 had

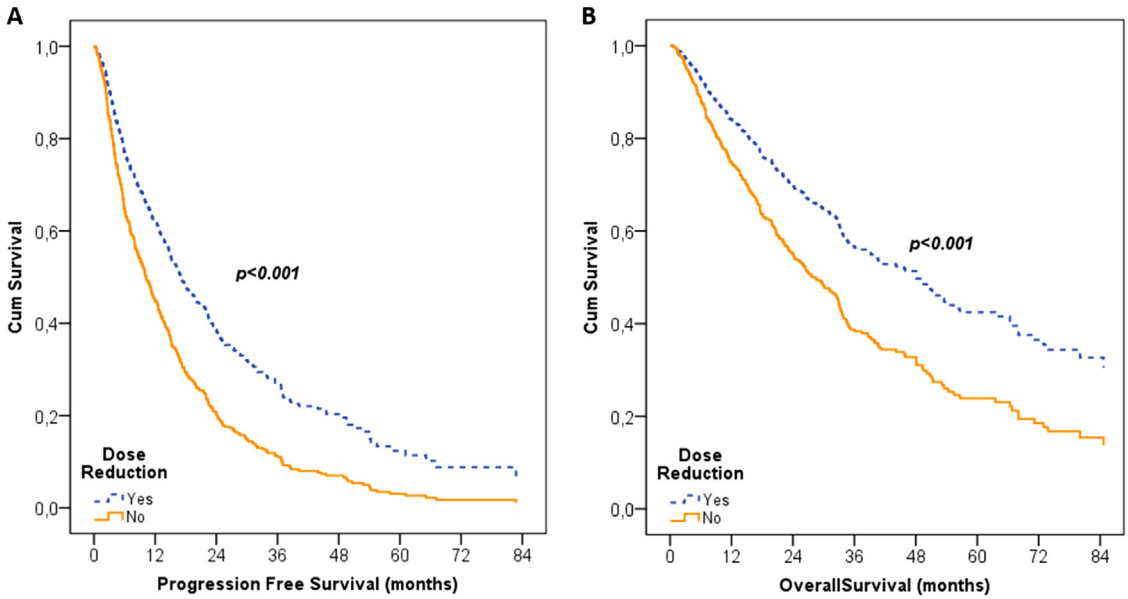

Fig. 2. Median (A) progression-free survival and (B) overall survival adjusted for IMDC prognostic group and nephrectomy in patients who reduced, or did not, initial treatment dose.

experienced a previous dose reduction. The median PFS was 5.3 months (95% CI: 3.8–6.7) for the first group and 6.1 months (95% CI: 2.6–9.5) for the second ($P = 0.3$) (Fig. 3C). The median OS was 13.2 months (95% CI: 6.8–19.6) for the first group and 21.4 months (95% CI: 15.7–27.2) for the second ($P = 0.4$) (Fig. 3D).

4. Discussion

This study reports that dose reductions related to adverse events during first-line therapy with sunitinib or pazopanib do not negatively affect the outcomes of mRCC patients. Previous evidence in the literature suggests a direct correlation between the dose intensity and the effectiveness of the therapy in patients [6]. An earlier pharmacokinetic/pharmacodynamics study investigated the relationships between sunitinib exposure in patients with advanced solid tumors and clinical outcomes, including in patients with gastrointestinal stromal tumors and metastatic renal cell carcinoma (mRCC). This particular study reported that the steady-state area under the curve of sunitinib plus its active metabolite was related to the time to tumor progression and OS. It was also reported that the dose was linked to a variety of investigated sunitinib side effects such as a rise in blood pressure and a drop in neutrophil numbers [6]. A prospective phase II study comparing 2 different sunitinib schedules (e.g., standard vs. 37.5 mg/d continuously) reported that the lower continued dose was clinically inferior compared to the standard dose in terms of PFS (7.1 vs. 9.9 months), with no improvement in safety. This suggested the superiority of the high-dose start approach [7]. More recently, an alternative sunitinib schedule (2 weeks on therapy followed by 1 week off) reported a longer period of PFS and a better safety profile in patients experiencing dose-limiting toxicity, even if the same result was not achieved when given as upfront treatment [8]. Taken together, this evidence suggests that the initial dose of sunitinib should be 50 mg, with a classic schedule of 4 weeks on followed by 2 weeks off, because any reduction of the initial dose is not supported by the same degree of effectiveness or a better safety profile.

In our study, we only included patients who started on a standard dose of sunitinib or pazopanib, and we found better outcomes for those receiving a reduced initial treatment dose because of toxicity. As reported, most patients reduce their treatment doses because of grade 2 toxicities. This is not unusual, because long-lasting low grade toxicity can negatively affect a patient's quality of life. The role of toxicity as a predictive factor in mRCC has been reported in previous studies. Meanwhile, a recent piece of work by our group analyzed the role of cumulative toxicity in mRCC patients treated with sunitinib or pazopanib [9,10]. Moreover, another study reported a better outcome for patients who continued treatment with personalized, reduced doses of sunitinib after initial toxicity compared to those treated with standard doses. Unfortunately, the population included in that study was largely heterogeneous, as only 60% of patients were treated during first-line therapy and a large number had a non–clear cell histology [11]. The results of our study are in accordance with those of a recent pooled analysis of the prognostic role of dose reduction in patients enrolled in 5 prospective trials involving sunitinib. However, unlike those findings, we are also able to confirm our results: on the basis of a landmark analysis that excluded the first 4 months of therapy; and in patients treated with pazopanib [12].

This data are in contrast to that of another article that analyzed the correlation between dose intensity and outcomes in

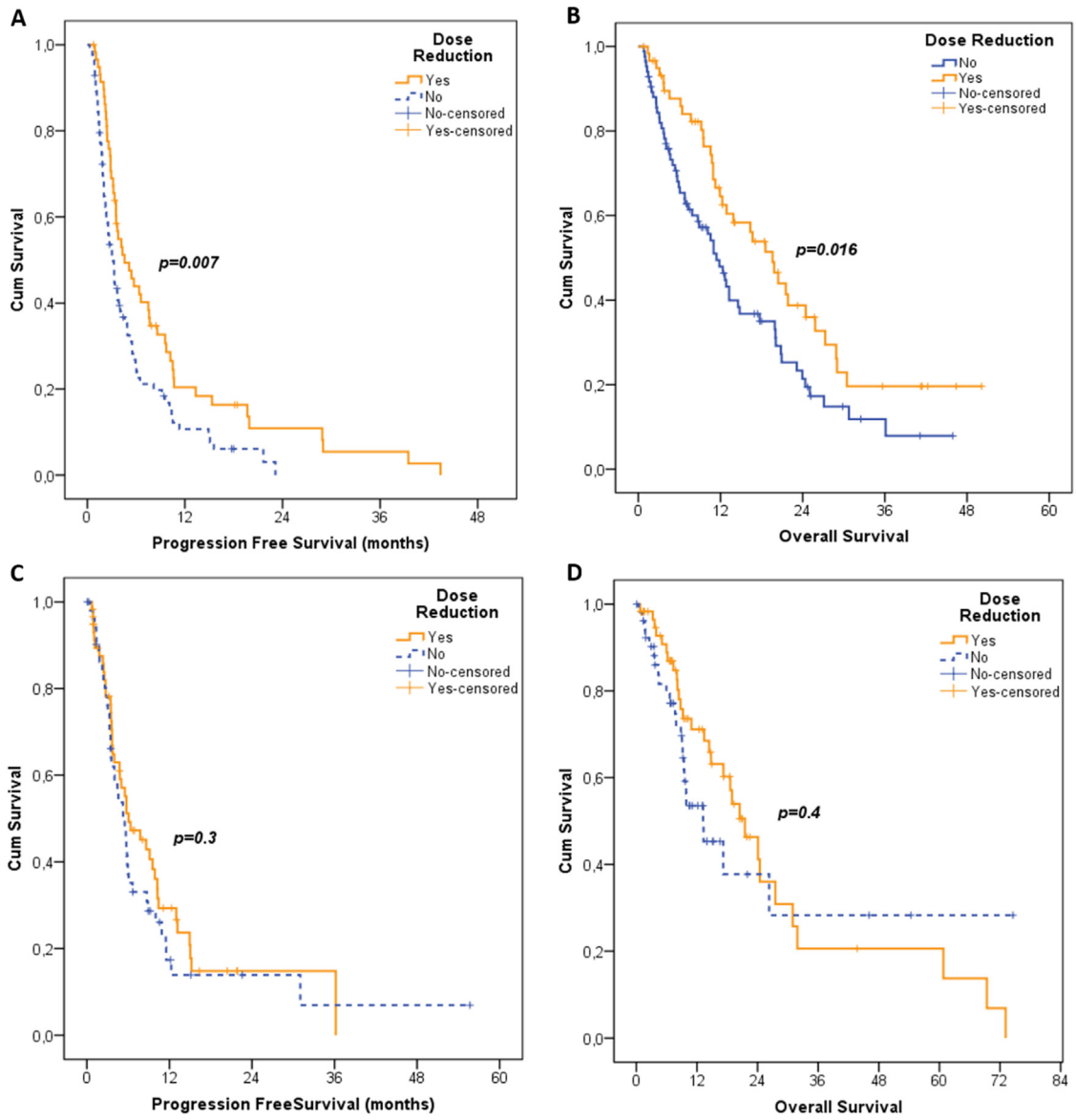

Fig. 3. Median progression-free survival and overall survival in patients who received second-line (A and B) mTOR or (C and D) tyrosine kinase inhibitors.

291 patients from 10 centers across Europe. The authors reported worse outcomes for patients with a lower dose intensity. A possible reason for this finding is that about 20% of these patients started with a lower dose of sunitinib [13]. De Velasco et al., who compared the different second-line outcomes of patients who discontinued first-line therapy because of disease progression or toxicity, reported similar data. Obviously, patients with progressive disease have worse outcomes than those who experience toxicity independent of the class of therapy used in second-line treatment [14].

Our study also reports that the increased PFS in patients who received reduced doses is related to an increased OS, even if the effects do not seem to influence the outcome of second-line treatment. In these patients, we reported that the previous dose reductions due to sunitinib- or pazopanib-related toxicity did not affect the outcome of treatment with a second VEGFR inhibitor, but these data may be due to the low number of patients included in the analysis. Meanwhile, previous toxicity seems to occur in patients who are more responsive to mTOR inhibitors. A possible explanation for our results is that toxicity and dose reductions are the epiphenomena of a tumor or patient phenotype, with increased sensitivity to targeted agents.

There are some limitations to our research owing to its retrospective nature. Data on patient comorbidities, concomitant medications, and attitudes to managing adverse events, which may have provided more insight, were not available. As the cases considered were treated from 2006 onwards, pazopanib and axitinib were not immediately available in Italy. Lastly, no prospective evaluation of progression was available, even though the AIFA registry dictates timings for clinical and radiological evaluations in

patients treated with high-cost drugs. The strengths of our study include the large cohort of unselected patients who were homogeneous for the type and dose of treatment at the start of therapy, and the analysis of several known factors that have a prognostic value in mRCC.

5. Conclusion

Dose reductions related to an adverse event during first-line treatment with sunitinib or pazopanib seem to be a positive prognostic factor. Our data need to be confirmed by prospective evidence, but could help physicians to select patients with a greater sensitivity to sunitinib or pazopanib for whom the initial dose could be reduced after toxicity without affecting survival and preserving a good quality of life.

Appendix A. Supplementary material

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1016/j.urolonc.2017.05.007.

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