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ORIGINAL RESEARCH

Prognostic factors in renal cell carcinoma patients treated with sorafenib: results from the Czech registry

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Abstract The aim of this study was to describe the characteristics and outcomes of a large cohort of patients treated with sorafenib in clinical practice and to identify predictive factors associated with prognosis. Patient data were obtained from the national Czech registry (RenIS). Data of virtually all Czech patients receiving targeted therapies are entered into this non-interventional post-registration database. Demographics and clinical data, as well as all treatment sequences and clinical outcomes, are reported in this registry. A total of 836 patients treated with sorafenib before March 2013 were included in the analysis. Median age was 63 years and 70 % were men. Most patients had received prior treatment with cytokines, sunitinib or both. Sorafenib was the first-line treatment in 15 % of patients. Median overall survival and progression-free survival were 21.7 months and 7.5 months, respectively. Median overall survival and progression-free survival was 26.3 and 8.3 months, respectively, in patients receiving sorafenib as first-line therapy. Cox proportional models identified several parameters associated with poor outcome including time ≤1 year from diagnosis to first-line systemic treatment, performance status ≥2, low hemoglobin, and LDH >1.5 times the upper limit of normal. Our data demonstrate that the outcomes of real-life patients are comparable to those enrolled in clinical trials. Prognostic factors identified in the present study were consistent with previously reported models.

Keywords Renal cell carcinoma · Metastasis · Targeted therapy · Outcomes · First-line therapy

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Introduction

Over 200,000 new patients with renal cell carcinoma (RCC) are diagnosed each year worldwide [1]. RCC predominantly affects men (2:1 ratio) and the median age at diagnosis is approximately 60 years [1]. The outcome of RCC is dependent of the disease stage at diagnosis, with the estimated 5-year survival rates of 96 % for patients diagnosed with stage I, 82 % for stage II, 64 % for stage III, and 23 % for stage IV RCC patients [2].

The principal therapeutic modality for localized and advanced RCC is surgical resection [1, 3, 4]. Systemic therapy is usually considered for patients presenting with unresectable or metastatic RCC (mRCC) [1, 3, 4]. Until recently, cytokines had been the only systemic therapy available for mRCC [5]. However, the activity of cytokines is limited. New targeted agents have been introduced to the management of mRCC over the last decade [6]. The oral multitargeted tyrosine kinase inhibitor sorafenib (Nexavar®) was one of the first targeted agents to demonstrate a statistically significant progression-free survival (PFS) benefit in mRCC [7–9]. Based on findings

from phase II and phase III trials, sorafenib was approved for the use in mRCC in 2005 in the USA and in 2006 in the European Union [10–12]. Sorafenib is recommended as second-line treatment after cytokine failure in patients with relapsed or medically unresectable stage IV predominantly clear cell RCC [3, 13]. It has also been used with some success in patients progressing on other targeted agents [14, 15].

The Czech Republic has reported the highest renal cancer and mortality in the world: incidence of 25 cases per 100,000 and mortality of 10 cases per 100,000. All Czech patients treated with targeted therapy are entered into a national registry "RenIS registry" and clinical outcomes are reported [16, 17]. This registry allows for the assessment and monitoring of patients treated with targeted agents in clinical practice. The aim of the present study was (i) to describe the characteristics and outcomes of patients treated with sorafenib in clinical practice, (ii) to compare the outcomes between the different lines of treatment, and (iii) to assess the prognostic factors based on the data from the national RenIS registry.

Patients and methods

The RenIS registry (Renal Information System, http://renis.registry.cz) is a non-interventional post-registration database of RCC patients treated with targeted agents in the Czech Republic. Seven targeted agents are currently approved and reimbursed in the Czech Republic, including sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab, pazopanib, and axitinib. The administration of targeted therapy is restricted to 20 specialized comprehensive cancer centers that accepted to participate in the registry. The project was initiated in June 2007 by the Czech Cancer Society. A detailed description of the RenIS registry has been published earlier [17].

All patients who started treatment with sorafenib before 25 March 2013 were included in the present analysis. Collected data included demographics, tumor characteristics, prior anticancer therapies, clinical parameters, and treatment response and outcomes. Fully anonymized patient data were entered into the database by the participating centers. The database has been approved by Ethical Committees of the participating centers.

Standard descriptive statistics were used to characterize the sample data set. Overall survival (OS) and progression-free survival (PFS) were the primary endpoints of this study. OS was defined as the time from sorafenib treatment initiation to death from any cause. PFS was defined as the time from sorafenib treatment initiation to progression or death from any cause. Both outcome measures were estimated using the Kaplan-Meier method. Statistical significance of the differences in Kaplan-Meier estimates was assessed with the log-rank test. Univariate and multivariate Cox proportional hazards models were used to evaluate the effect of all potential predictive and prognostic factors on the survival measures. Hazard ratio was estimated with appropriate 95 % confidence intervals (CI) and significance levels.

Results

Demographics and patient characteristics

A total of 836 patients treated with sorafenib were included in the present analysis. Baseline characteristics are shown in Table 1. Median age at the initiation of sorafenib was 63 years. Most patients were men (70 %).

Table 1 Demographics and clinical characteristics

Characteristics	*n*=836
Male, *n* (%)	588 (70.3)
Age at diagnosis	
Median, (min–max)	59 (21–83)
Age at targeted therapy initiation, years	
Median, (min–max)	63 (22–83)
Time from diagnosis to first-line treatment, *n* (%)	
≤1 year	441 (52.8)
Morphology, *n* (%)	
Clear cell carcinoma	800 (95.7)
Papillary cell carcinoma	29 (3.5)
Chromophobe cell carcinoma	5 (0.6)
Unknown	2 (0.2)
Disease status at diagnosis, *n* (%)	
Metastatic	385 (46.1)
Localized/locally advanced	370 (44.3)
Unknown/not stated	81 (9.7)
Metastasis at targeted therapy initiation, *n* (%)	814 (97.4)
Prior nephrectomy, *n* (%)	738 (88.3)
Prior immunotherapy, *n* (%)	648 (77.5)
Prior radiotherapy, *n* (%)	179 (21.4)
Prior targeted therapy, *n* (%)	290 (34.7)
Performance status (PS) at sorafenib initiation[b]	
0	165 (22.0)
1	488 (65.2)
2 or 3	96 (12.8)
Calcium[a] >2.5 mmol/l, *n* (%)	53 (12.5)
LDH[a] >1.5× ULN, *n* (%)	43 (13.4)
Thrombocytes[a] >400×10^9/l, *n* (%)	84 (15.6)
Hemoglobin[a] <LLN, *n* (%)	301 (55.7)
Neutrophils[a] >7×10^9/l, *n* (%)	40 (9.5)

LLN lower limit of normal, *ULN* upper limit of normal

[a] Laboratory parameters at the time of sorafenib initiation are calculated using the number of patients with available values

[b] PS at sorafenib initiation is known in 749 (90 %) patients

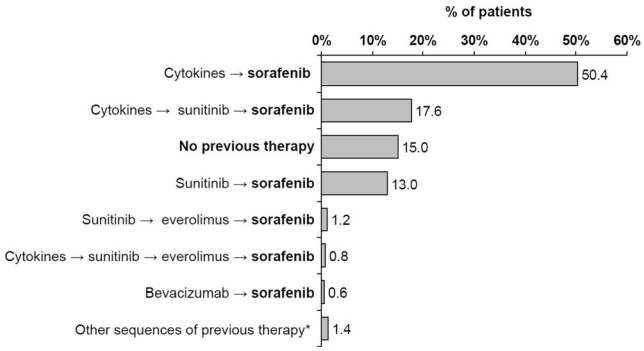

Fig. 1 Sequences of therapies in patients receiving sorefanib. *Asterisk* indicates other sequences include all sequences observed in three or less patients

Clear cell carcinoma was the most frequent histology (96 %). Almost half of patients had synchronous metastases at diagnosis and 97 % at the time of targeted therapy initiation.

Nephrectomy was performed in 88 % (n=738) of patients. Most patients received prior immunotherapy (n=648; 78 %) as neoadjuvant and palliative therapy. Of these patients, 62 % (n=522) received interferon-α monotherapy (between 5 and 9 MIU three times weekly) and 13 % (n=110) received an interleukin-2, interferon-α, and 5-fluorouracil combination.

Table 2 Sorafenib treatment and therapeutic outcomes

Characteristics	n=836
Sorafenib treatment duration, months	
Median, (5th–95th percentile range)	5.2 (0.5–22.9)
Line of treatment, *n* (%)	
1st line	125 (15.0)
2nd line	541 (64.7)
3rd line	161 (19.3)
4th line	9 (1.1)
Initial daily dose of sorafenib[a], *n* (%)	
800 mg	630 (75.9)
600 mg	29 (3.5)
500 mg	2 (0.2)
400 mg	124 (14.9)
200 mg	45 (5.4)
Patients who discontinued sorafenib, *n* (%)	758 (90.7)
Reasons for sorafenib discontinuation, *n* (%)	
Disease progression	511 (67.4)
Adverse events	132 (17.4)
Other	115 (15.2)
Response to sorafenib, *n* (%)	
Complete remission	17 (2.0)
Partial remission	140 (16.7)
Stable disease	280 (33.5)
Progressive disease	245 (29.3)
Not available	154 (18.5)

[a] Initial daily dose is known in 830 (99 %) patients

Almost one third (n=290; 35 %) received prior targeted therapy (Fig. 1).

At the time of sorafenib initiation, 165 patients (22 %) were asymptomatic (performance status [PS] 0), 488 (65 %) had minimal symptoms (PS 1), and 96 (13 %) had poor performance status (PS ≥2).

Sorafenib treatment

Details on sorafenib administration and therapeutic response are summarized in Table 2. Sorafenib was used as first-line treatment in 15 % (n=125) of patients and as second-line treatment in 65 % (n=541). The prescribed dose was 800 mg orally in two daily doses in most patients (n=630; 76 %). Median duration of sorafenib treatment was 5.2 months in all patients.

As of the cutoff date for this analysis, treatment with sorafenib was discontinued in 91 % (n=758) of patients. The most common reasons for sorafenib discontinuation was disease progression (n=511; 67 %) and occurrence of adverse events (n=132; 17 %).

Complete and partial remissions were observed in 2 % (n=17) and 17 % (n=140) of all patients, respectively. Stable disease was reported in 34 % (n=280) of patients. The response was not evaluable in 154 patients (19 %).

During sorafenib treatment, adverse events were reported in 405 patients (48 %). Of these, 122 experienced serious adverse events. Main reported adverse events were skin toxicity (28 %) and gastrointestinal complications (19 %) (Table 3).

Overall survival (OS) and progression-free survival (PFS)

As of 25 March 2013, 446 patients (53 %) died and 138 (17 %) were lost to follow up. Median OS and median PFS

Table 3 Listing of all adverse events reported during the use of sorafenib

	n (%)
All reported adverse events	405 (48.4)
All serious adverse events	122 (14.6)
Nature of adverse events	
Skin toxicity	235 (28.1)
Gastrointestinal	155 (18.5)
Cardiovascular	58 (6.9)
Hematologic	25 (3.0)
Metabolic	21 (2.5)
Neurologic	18 (2.2)
Respiratory	13 (1.6)
Musculoskeletal	13 (1.6)
Fatigue	10 (1.2)
Other	45 (5.4)

was 21.7 and 7.5 months, respectively. One- and 2-year OS rates were 69.0 % (95 % confidence interval (CI): 65.7–72.4) and 47.5 % (95 % CI: 43.7–51.4), respectively. One- and 2-year PFS were 34.1 % (95 % CI: 30.8–37.5) and 16.3 % (95 % CI: 13.6–19.1), respectively. OS and PFS results with Kaplan-Meier survival curves are shown in Fig. 2.

OS and PFS were also analyzed according to the prior treatment. Median OS was significantly better in patients having received no prior therapy or prior cytokines only compared with those with prior sunitinib only or prior cytokines and sunitinib treatment. One-year OS rates were 71.6 % (95 % CI: 63.2; 80.0) and 72.3 % (95 % CI: 67.8–76.8) in patients with no prior therapy and in patients having received prior cytokines only, respectively. Similarly median PFS was significantly longer in patients having received no prior therapy or prior cytokines only. OS and PFS results according to the line of treatment are summarized in Table 4. Kaplan-Meier survival curves are shown in Fig. 3 according to the line of treatment.

Assessment of predictive factors for OS and PFS

In the univariate Cox analysis, factors significantly associated with inferior OS included absence of nephrectomy, stage IV disease at diagnosis, time from diagnosis to first-line systemic treatment initiation ≤1 year, PS ≥1, hemoglobin < lower limit of normal (LLN), LDH >1.5× the upper limit of normal (ULN), thrombocytes $>400\times10^9$/l, and neutrophils $>7\times10^9$/l (Table 5). There was a borderline significant association of poor OS with calcium >2.5 mmol/l. All parameters, with the exception of the stage at diagnosis, were then entered into a multivariate model (Table 6). The stage at diagnosis was highly correlated with the time from diagnosis to first-line treatment, and this parameter was not included in the multivariate model. Subsequent multivariate analysis identified five factors that were independently predictive for poorer OS in patients treated with sorafenib: time from diagnosis to first-line systemic therapy ≤1 year, Eastern Cooperative Oncology Group Performance Status (ECOG) PS 1, hemoglobin < LLN, LDH >1.5× ULN, and neutrophil count $>7\times10^9$/l. Given the limited number of patients with available laboratory values, this model was based on data from only 259 patients (31 %). Therefore, another model excluding the laboratory values was planned (n=749; 90 % patients). In this latter model, three factors were identified as independent predictors of worse OS, including time from diagnosis to first-line therapy ≤1 year, sorafenib as third- or fourth-line treatment, and ECOG PS ≥1.

Factors significantly associated with inferior PFS included time from diagnosis to first-line systemic treatment initiation ≤1 year, poor PS, hemoglobin < LLN, LDH >1.5× ULN, thrombocytes $>400\times10^9$/l, and neutrophils $>7\times10^9$/l (Table 5). Again, there was a borderline significant trend towards the worse PFS in patients with calcium >2.5 mmol/l. As for the OS, two multivariate Cox models were calculated that either included or excluded laboratory parameters. In the first model (n=259), four parameters found to independently predict inferior PFS included time from diagnosis to first-line therapy ≤1 year, sorafenib as third- or fourth-line treatment, poor ECOG PS (1–3), and LDH >1.5× ULN. Among these four parameters that were significantly predictive of PFS in the first model, the first three variables were also significant predictors of PFS in the second model (Table 7).

Discussion

The present analysis issued from a national population-based registry reflects the clinical practice and the management of patients with metastatic RCC. The results show that the efficacy and safety of sorafenib in real-life practice in the Czech Republic are comparable, or slightly better, than the outcomes observed in selected patients enrolled in clinical trials. This observation may reflect the patient selection process in a health-care system with limited resources. Improved management of side effects and availability of active agents for

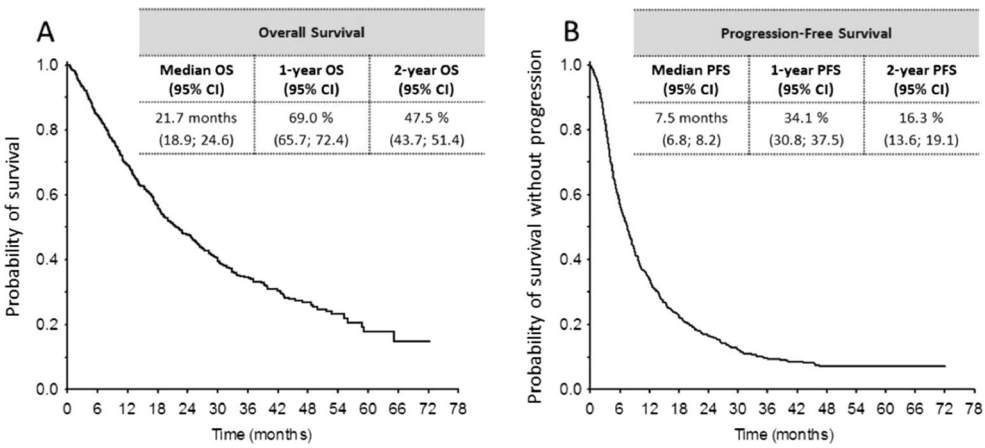

Fig. 2 Overall survival (**a**) and progression-free survival (**b**) in all patients treated with sorafenib

Table 4 Overall survival (OS) and progression-free survival (PFS) from sorafenib treatment initiation according to the prior treatment

Prior therapy	*n*	Median OS (95 % CI)	1-year OS (95 % CI)	2-year OS (95 % CI)	Log-rank test *p* value
No prior therapy	125	26.3 months (17.5; 35.1)	71.6 % (63.2; 80.0)	52.4 % (42.5; 62.4)	0.001
Prior cytokines only	421	25.0 months (21.4; 28.5)	72.3 % (67.8–76.8)	51.6 % (46.2–57.0)	
Prior sunitinib only	109	18.1 months (14.7; 21.4)	62.2 % (52.5–71.9)	36.3 % (25.3–47.3)	
Prior cytokines→sunitinib	147	17.1 months (14.0; 20.2)	60.9 % (52.8–69.0)	37.2 % (28.4–46.0)	
Prior therapy		Median PFS (95 % CI)	1-year PFS (95 % CI)	2-year PFS (95 % CI)	Log-rank test *p* value
No prior therapy	125	8.3 months (6.3; 10.3)	39.0 % (30.0; 48.0)	17.4 % (13.5–21.3)	0.001
Prior cytokines only	421	8.6 months (7.7; 9.6)	39.1 % (34.3–43.9)	19.3 % (11.7–26.8)	
Prior sunitinib only	109	5.2 months (3.9; 6.5)	23.0 % (14.8–31.2)	9.8 % (3.4–16.1)	
Prior cytokines→sunitinib	147	5.7 months (4.1; 7.3)	24.5 % (17.4–31.6)	14.2 % (8.2–20.2)	

patients failing sorafenib treatment might have contributed to better outcomes. Since targeted therapy is provided by restricted number of centers in the Czech Republic, the patients are therefore thoroughly followed by the oncologists, without substantial involvement of the general practitioners, allowing for close monitoring and reporting of adverse events and complications.

The present data showed also that the use of sorafenib in the Czech Republic was generally in accordance with the European and US guidelines [3, 13]. No particular safety concerns were raised regarding the use of sorafenib. Almost all patients treated with sorafenib had clear cell RCC. The majority of patients received sorafenib as second-line treatment after cytokines or after sunitinib (65 %), while 20 % were treated in the third-line or higher after cytokines and sunitinib. A minor, but non-negligible proportion of patients were treated with sorafenib as first-line treatment. Clinical outcomes, including OS and PFS, were significantly better in patients on first-line treatment or second-line treatment after cytokines compared with other treatment sequences.

In a recent phase III randomized trial evaluating the efficacy and safety of sorafenib versus axitinib, a second-generation VEGFR inhibitor, as first-line treatment in patients with mRCC, PFS was comparable between groups [18]. Other studies showed also that PFS and OS were not significantly different between the sorafenib and sunitinib groups, as first-line treatment for patients with mRCC [19]. The recently completed phase III SWITCH study showed that the sequence sorafenib-sunitinib is equivalent to sunitinib-sorafenib, in terms of OS and combined PFS [20]. Sorafenib has also shown activity in other randomized studies, including those patients progressing on sunitinib [21] and on VEGF-targeted agent or a mammalian target of rapamycin (mTOR) inhibitors [15]. These reported results together with our results suggest that sorafenib might be a fair alternative as a VEGF-targeted therapy for the second and later lines and possibly even in the first line.

Given the fact that sunitinib and sorafenib were the first two targeted agents for mRCC introduced in the Czech Republic, it is not surprising that most patients receiving sorafenib were also treated, in sequence with sunitinib. Of note, the optimal sequence for sorafenib and sunitinib was recently evaluated in mRCC [22]; the sorafenib-sunitinib sequence reported a longer combined PFS compared with the sunitinib-sorafenib sequence. In general, physicians would feel more confident prescribing sorafenib and sunitinib, than newly discovered agents; which may explain the use of sorafenib as a first-line treatment in a number of patients (15 %),

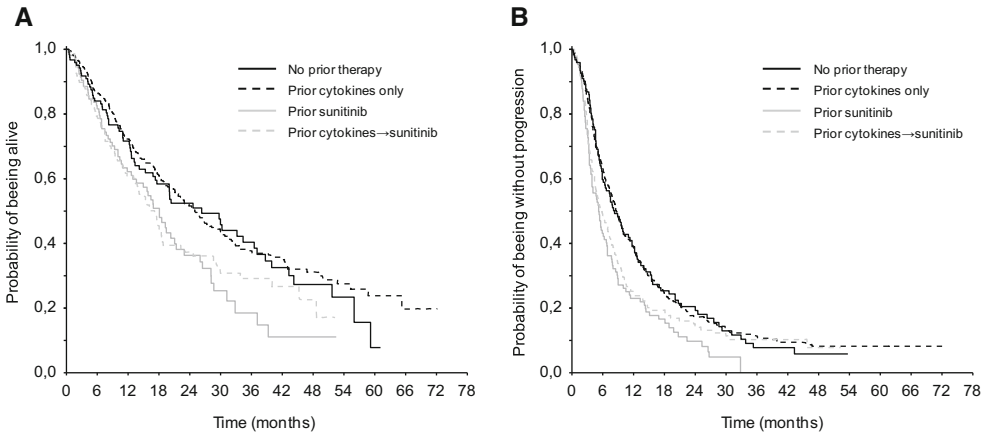

Fig. 3 Overall survival (**a**) and progression-free survival (**b**) in patients treated with sorafenib according to the prior treatment. The overall survival (**a**) and the progression-free survival (**b**) were significantly different according to the prior treatment: $p=0.001$ and $p<0.001$, respectively

Table 5 Univariate analysis of parameters predictive for OS and PFS in patients treated with sorafenib

	Variables	*N*	OS		PFS	
			HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Sex	Female vs. male	248/588	1.00 (0.82; 1.23)	0.970	0.95 (0.81; 1.12)	0.551
Age	≥65 years vs. <65 years	344/492	0.91 (0.75; 1.10)	0.323	0.94 (0.80; 1.09)	0.408
Prior nephrectomy	Yes vs. no	738/98	0.61 (0.46; 0.81)	<0.001	0.80 (0.64; 1.01)	0.065
Stage at diagnosis	Stage IV vs. stage I–III	385/370	1.35 (1.11; 1.64)	0.003	1.16 (0.99; 1.36)	0.060
Time from diagnosis to first-line therapy	≤1 year vs. >1 year	441/395	1.57 (1.30; 1.90)	<0.001	1.38 (1.19; 1.61)	<0.001
Line of sorafenib	3rd or 4th line vs. 1st line	170/125	1.29 (0.94; 1.76)	0.119	1.22 (0.94; 1.57)	0.133
	2nd line vs. 1st line	541/125	0.99 (0.76; 1.30)	0.943	1.07 (0.86; 1.33)	0.543
ECOG PS	PS2 or 3 vs. PS0	96/165	2.26 (1.63; 3.15)	<0.001	1.90 (1.43; 2.51)	<0.001
	PS1 vs. PS0	488/165	1.52 (1.18; 1.97)	0.001	1.51 (1.23; 1.85)	<0.001
Calcium	>2.5 mmol/l vs. ≤2.5 mmol/l	53/371	1.45 (1.00; 2.09)	0.050	1.36 (1.00; 1.86)	0.052
LDH	>1.5× ULN vs. ≤1.5× ULN	301/239	1.63 (1.12; 2.37)	0.011	1.58 (1.13; 2.20)	0.007
Thrombocytes	$> 400\times10^9$/l vs. $\leq 400\times10^9$/l	43/279	1.63 (1.21; 2.19)	0.001	1.43 (1.11; 1.84)	0.005
Hemoglobin	<LLN vs. ≥LLN	84/456	1.71 (1.34; 2.17)	<0.001	1.63 (1.34; 1.96)	<0.001
Neutrophils	$> 7\times10^9$/l vs. $\leq 7\times10^9$/l	40/380	2.14 (1.42; 3.21)	<0.001	1.56 (1.10; 2.21)	0.012

OS overall survival, *PFS* progression-free survival, *HR* hazard ratio, *CI* confidence interval

although it is not commonly recommended. Data from other analyses based on the RenIS registry showed that over 10 % of patients were treated with everolimus in second- or third-line setting. Bevacizumab and temsirolimus were rarely administered. It should be noted that reimbursement of pazopanib and axitinib was approved in the Czech Republic only in 2011 and 2013, respectively.

Compared with the general population of Czech patients diagnosed with RCC, this analysis revealed that sorafenib tended to be administered to younger patients, indicating possible patient selection. According to the epidemiological data from the Czech National Cancer Registry [23], almost 53 % of patients are aged over 65 years at diagnosis, while in the present report, the proportion of patients aged over 65 years at sorafenib treatment initiation was lower (41 %). The majority of patients had a good performance status at sorafenib initiation (PS 0–1).

Table 6 Multivariate analyses of parameters predictive for OS using model that includes or excludes laboratory parameters

	Variables	Model 1			Model 2		
		N	HR (95 % CI)	*p* value	*N*	HR (95 % CI)	*p* value
Sex	Female vs. male	81/178	0.98 (0.68;1.42)	0.912	221/528	0.92 (0.74;1.14)	0.441
Age	≥65 years vs. <65 years	111/148	0.89 (0.62; 1.26)	0.510	314/435	0.95 (0.77; 1.16)	0.605
Prior nephrectomy	Yes vs. no	229/30	0.63 (0.39; 1.04)	0.072	660/89	0.76 (0.57; 1.03)	0.077
Time from diagnosis to 1st line	≤1 year vs. >1 year	147/112	1.56 (1.08; 2.25)	0.019	400/349	1.59 (1.28; 1.97)	<0.001
Line of sorafenib	3rd or 4th line vs. 1st line	54/28	1.40 (0.76; 2.57)	0.281	127/125	1.44 (1.03; 2.02)	0.035
	2nd line vs. 1st line	177/28	0.81 (0.47; 1.42)	0.469	497/125	0.94 (0.71; 1.25)	0.681
ECOG PS	PS 2–3 vs. PS 0	30/64	1.71 (0.89; 3.28)	0.108	96/165	2.32 (1.65; 3.26)	<0.001
	PS1 vs. PS 0	165/64	1.62 (1.08; 2.45)	0.021	488/165	1.55 (1.19; 2.00)	0.001
Calcium	>2.5 mmol/l vs. ≤2.5 mmol/l	29/230	1.28 (0.77; 2.13)	0.348	–	–	–
Hemoglobin	<LLN vs. ≥LLN	149/110	1.42 (1.00; 2.02)	0.048	–	–	–
LDH	>1.5× ULN vs. ≤1.5× ULN	31/228	2.06 (1.29; 3.28)	0.003	–	–	–
Thrombocytes	$>400\times10^9$ vs. $\leq 400\times10^9$/l	53/206	1.00 (0.66; 1.50)	0.987	–	–	–
Neutrophils	$>7\times10^9$ vs. $\leq 7\times10^9$/l	28/231	1.77 (1.08; 2.91)	0.024	–	–	–

OS overall survival, *PFS* progression-free survival, *HR* hazard ratio, *CI* confidence interval

Table 7 Multivariate analyses of parameters predictive for PFS using model that includes or excludes laboratory parameters

	Variables	Model 1			Model 2		
		N	HR(95 % CI)	*p* value	*N*	HR(95 % CI)	*p* value
Sex	Female vs. male	81/178	0.90 (0.65; 1.24)	0.510	221/528	0.86 (0.72; 1.03)	0.094
Age	≥65 years vs. <65 years	111/148	0.89 (0.66; 1.2)	0.447	314/435	0.98 (0.83; 1.16)	0.832
Prior nephrectomy	Yes vs. no	229/30	0.82 (0.54; 1.26)	0.366	660/89	1.00 (0.77; 1.28)	0.970
Time from diagnosis to 1st line	≤1 year vs. >1 year	147/112	1.43 (1.05; 1.94)	0.023	400/349	1.44 (1.22; 1.71)	<0.001
Line of sorafenib	3rd or 4th line vs. 1st line	54/28	1.98 (1.17; 3.34)	0.011	127/125	1.41 (1.06; 1.86)	0.017
	2nd line vs. 1st line	177/28	1.17 (0.73; 1.87)	0.526	497/125	1.05 (0.84; 1.32)	0.657
ECOG PS	PS 2–3 vs. PS 0	30/64	1.96 (1.15; 3.33)	0.013	96/165	2.04 (1.53; 2.73)	<0.001
	PS1 vs. PS 0	165/64	1.59 (1.12; 2.25)	0.010	488/165	1.58 (1.29; 1.94)	<0.001
Calcium	>2.5 mmol/l vs. ≤2.5 mmol/l	29/230	1.49 (0.95; 2.34)	0.083	–	–	–
Hemoglobin	<LLN vs. ≥LLN	149/110	1.29 (0.96; 1.72)	0.088	–	–	–
LDH	>1.5× ULN vs. ≤1.5× ULN	31/228	1.66 (1.08; 2.54)	0.021	–	–	–
Thrombocytes	$>400\times10^9$ vs. $\leq400\times10^9$/l	53/206	1.08 (0.76; 1.54)	0.675	–	–	–
Neutrophils	$>7\times10^9$ vs. $\leq7\times10^9$/l	28/231	1.18 (0.76; 1.85)	0.461	–	–	–

The present strategy of mRCC management is, to a large extent, determined by patient stratification. The Memorial Sloan-Kettering Cancer Center (MSKCC) model is the most widely used prognostic system [3, 13]. This model, established by Motzer et al., classifies patients according to the presence or absence of five adverse prognostic factors, including Karnofsky performance status of 70 or less, serum LDH level greater than 1.5× ULN, low hemoglobin level, corrected serum calcium level above the ULN, and time from diagnosis and nephrectomy to therapy of less than 1 year [24]. Another study confirmed the validity of this model in patients treated with targeted agents [25]. Independent prognostic parameters identified in the present study are almost identical to MSKCC criteria, despite the fact that the population in the present analysis was very heterogeneous, with most patients pre-treated with different agents and only a minority received sorafenib as first-line treatment.

However, our study has some limitations, including the retrospective design and the number of missing data, particularly in laboratory values. Like other retrospective studies, a potential selection bias could not be excluded. The treatment was administered at the discretion of the attending medical oncologist in the centers, and there was no source data verification. Consequently, the data on progression-free survival may be biased, while the data on overall survival that are checked against the national database of deaths must be considered as reliable. On the other hand, the strength of this study was its ability to reproduce the outcomes observed in prospective trials. Despite all these potential biases, these real-world results acquired from a nationwide Czech registry could be useful either for comparing the routine practice with trials results or for generating valuable hypotheses.

In conclusion, the present data describe the use of sorafenib in the management of mRCC in clinical practice. The outcomes of real-life patients, including PFS and OS data, were comparable to those achieved in prospective trials [4, 8, 26, 27].

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