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Results and analysis of the application of a consistent targeted therapy in patients with metastatic renal cell carcinoma in Moscow (for the period from June 2005 to July 2015)

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Background. *This article is a personal experience of a sequential targeted therapy of tyrosine kinase inhibitors for the period from June 2005 to July 2015.*

Objective*: evaluation of the results of the consistent application of targeted therapies in Moscow in this period.*

Materials and methods. *A retrospective analysis of cumulative progression-free survival in 220 patients of 354 patients with mRCC were studied. Was used Statistica 10.0 program.*

Results. *This article presents an analysis of the effectiveness of treatment and survival of patients receiving this therapy in cancer institutions Department of Health in Moscow.*

Conclusion. *Using of targeted therapy scheme sunitinib → sorafenib, we see no significant difference sVBP compared with scheme sorafenib → sunitinib with two lines of sequential therapy tyrosine kinase inhibitors (16.9 and 18.2 months). According to our data total progression-free survival terms as applied to the 1st line of therapy tirosine kinase inhibitors (sunitinib and sorafenib), followed by the appointment pazopanib in the 2nd line (12.5 and 14.4 months) and pazopanib in 1st line followed by the appointment tirazinkinaz inhibitors (sunitinib and sorafenib) in the 2nd line (12.50 and 11.56 months) compared to the preliminary results of a multicenter randomized trial expected SWITCH II also not statistically different.*

Key words: *kidney cancer, sequential targeted therapy, metastases, tyrosine kinase inhibitors*

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Introduction

Discoveries in molecular and clinical oncology, extraordinary developments in genetic research fundamentally changed doctors' approach to treatment of patients with metastatic renal cell carcinoma (mRCC). In the last 15–20 years scientists' efforts have brought into clinical practice about twenty specific molecular inhibitors suppressing cancer signaling pathways (targeted drugs). More than a hundred of targeted agents are currently being tested in clinical studies [1]. Thus far, there are no generally accepted paradigm and single concept of sequence of targeted drugs in the treatment of mRCC due to time limits of their effectiveness. Nevertheless, targeted therapy allowed to translate mRCC into a chronic disease and increase overall survival of patients with kidney cancer and distant metastases by years [2].

Renal cell carcinoma (RCC) morbidity is growing steadily around the world, and it has the second highest rate of increase after malignant tumors of the central nervous system. Moreover, disease progression after radical surgical treatment – metastasis – is observed in 20–40 % of patients [3, 4].

Currently, Russian cancer urologists have 7 targeted drugs at their disposal (bevacizumab, sorafenib, sunitinib, pazopanib, axitinib, temsirolimus, everolimus). These drugs interact with certain receptors, and presence of these receptors in the tumor allow to predict treatment effectiveness. In order to improve clinical effect, it is important to understand the sequence of administration of targeted drugs in the treatment of mRCC.

Success and effectiveness of administration of these drugs are accompanied by a number of problems, including different side effects and high cost of the therapy [5]. An optimal sequence of targeted drugs for treatment of patients with RCC metastases will allow to delay development of drug tolerance and improve patient survival [5, 6].

Study objective: To share our experience and retrospectively evaluate results of sequential targeted therapy (multichannel blockers) in Moscow: sorafenib with subsequent administration of sunitinib, sunitinib with subsequent administration of sorafenib, as well as sorafenib → pazopanib, sunitinib → pazopanib, pazopanib → sunitinib, and pazopanib → sorafenib sequences in patients with mRCC.

Materials and methods

Our study isn't a clinical trial, but a retrospective comparative analysis of sequential targeted therapy in patients with mRCC in the context of Russian healthcare (in particular, in Moscow). Patients (806 people) were very diverse, patient groups weren't balanced and selected depending on specific characteristics (age, sex, ECOG and Karnofsky scales' performance status, morphological tumor variant, metastases localization, et al.) which was done in many studies, including the SWITCH multicenter randomized phase III study, where mRCC patients with favorable or moderate prognosis per MSKCC criteria (Memorial Sloan-Kettering Cancer Centre), ECOG, without previous treatment, were randomized into 2 groups. Characteristics of patients in the groups receiving targeted agents corresponded to those of routine clinical

practice. Targeted therapy was administered in 354 (43.92 %) of 806 patients.

Data on the lines and relative duration of sequential targeted therapy are presented in Table 1. In some lines, we didn't measure duration of administration due to small number of patients and short period of administration, but treatment and follow-ups, as well as patient enrolment, continue. Cumulative progression-free survival (cPFS) was calculated using the Kaplan-Meier estimator.

Table 1 presents different sequences of targeted drugs we used. In the majority of cases of sequential targeted therapy, the 1st targeted drug (tyrosine kinase inhibitor) was changed to a drug of the same type. We performed a detailed analysis of treatment duration in the first 6 patient groups ($n = 220$; 62.15 %). Patient characteristics for these groups are presented in Table 2.

Patient data play an important role in personalization of mRCC treatment. In many randomized trials ECOG performance status and MSKCC risk group are taken into account [7]. Age distribution of patients should be considered because of a significant number of coexisting disorders in older patients and possibility of severe side effects. Older patients' inclusion into studies is limited [7]. In our retrospective analysis, we didn't always note the ECOG status and MSKCC risk during therapy prescription (see Table 2) because this patient cohort received treatment in various Moscow medical institutions under supervision of different doctors, and in every case the therapy was prescribed individually based on available information about the patient, various characteristics, and advancement of metastatic process.

Treatment of kidney cancer metastases – active surgical tactic, targeted therapy, or radiation therapy – is still a subject of discussion. We advocate for aggressive approach, especially for solitary and single metastases, using combination therapy. Therefore, in every possible, advisable, and necessary case we tried to perform metastasectomy accompanied by targeted therapy or external beam therapy (EBT). Characteristics of patients who received EBT are presented in Table 3.

Table 4 presents types of surgeries performed in the patients receiving sequential targeted therapy. Interventions can be divided into 2 groups: metastasectomies and surgeries to improve quality of life.

Table 1. *Lines of sequential targeted therapy*

Targeted therapy sequence	Number of patients, *n* (%)	Progression-free survival, months
Sorafenib → sunitinib	85 (10.55)	16.9
Sunitinib → sorafenib	35 (4.34)	18.2
Sunitinib → pazopanib	32 (3.97)	14.4
Pazopanib → sunitinib	25 (3.10)	11.56
Sorafenib → pazopanib	31 (3.84)	12.5
Pazopanib → sorafenib	12 (1.49)	12.5
Bevacizumab → sorafenib	21 (2.60)	–
Bevacizumab → sunitinib	19 (2.35)	–
Bevacizumab → pazopanib	4 (0.50)	–
Bevacizumab → everolimus	1 (0.12)	–
Everolimus → pazopanib	3 (0.36)	–
Everolimus → sorafenib	1 (0.12)	–
Everolimus → sunitinib	2 (0. 24)	–
Everolimus → bevacizumab	1 (0.12)	–
Everolimus → bevacizumab	5 (0.60)	–
Sunitinib → everolimus	14 (1.74)	–
Sunitinib → axitinib	1 (0.12)	–
Sorafenib → bevacizumab	16 (2.0)	–
Sorafenib → everolimus	21 (2.6)	–
Sorafenib → temsirolimus	2 (0.24)	–
Sorafenib → tivozanib	1 (0.12)	–
Axitinib → sunitinib	4 (0.48)	–
Temsirolimus → sunitinib	7 (0.87)	–
Pazopanib → axitinib	1 (0.12)	–
Pazopanib → temsirolimus	1 (0.12)	–
Pazopanib → bevacizumab	1 (0.12)	–
Pazopanib → everolimus	8 (0.99)	–
Total	*354 (100)*	

Application of sorafenib → sunitinib and sunitinib → sorafenib sequential targeted therapy

Number of patients receiving sorafenib as the 1st line therapy and sunitinib as the 2nd was 85 (24.0 %), number of patients receiving sunitinib as the 1st line and then sorafenib was 35 (9.89 %). Detailed characteristics of the patient groups and comparison with the SWITCH study are presented in Table 2. In this cohort 13 patients underwent EBT of metastatic lesions: 9 (10.59 %) patients were in the sorafenib → sunitinib group (1st group) and 4 (11.43 %) were in the sunitinib → sorafenib group (2nd group) (see Table 3).

Evaluation of the results of sequential therapies in the sorafenib → sunitinib and sunitinib → sorafenib groups has shown that cPFS was 16.9 months in the 1st group and 18.2 months in the 2nd group. These are satisfactory survival times. There are several reasons for this: non-compliance with the schedule of control examinations due

to circumstances (we couldn't always perform examinations (computed tomography and magnetic resonance imaging) at the planned time due to limited capacity of diagnostics departments); inclusion of patients without considering specific characteristics, ECOG and MSKCC scores; and use of combination therapy (surgery and radiation) alongside targeted therapy to treat RCC metastases in many patients. Estimation of duration of targeted drugs administration in the sequential lines of mRCC therapy and comparison with the SWITCH data are presented in Figure 1.

Application of sorafenib → pazopanib and sunitinib → pazopanib sequential targeted therapy

Here we present use of the following sequential targeted therapy lines: sorafenib → pazopanib (n = 31) and sunitinib → pazopanib (n = 32) (see Table 2).

Among these patients 7 received EBT: 3 (9.67 %) in the sorafenib → pazopanib group and 4 (12.50 %) in the sunitinib → pazopanib group (see Table 3). In advisable cases, metastasectomies and surgeries to improve quality of life were performed (see Table 4).

Estimation of the duration of targeted drugs administration in sequential lines of mRCC therapy is presented in Figure 2.

Application of pazopanib → sorafenib and sorafenib → pazopanib, sunitinib → pazopanib and pazopanib → sunitinib sequential targeted therapies

Currently, the SWITCH II multicenter randomized study of sorafenib → pazopanib and pazopanib → sorafenib sequential targeted therapies is coming to an end, but final data aren't yet available, preliminary data are expected. We present our results for the sorafenib → pazopanib (n = 31) and pazopanib → sorafenib (n = 12), as well as sunitinib → pazopanib (n = 32) and pazopanib → sunitinib (n = 25) sequential schedules (see Table 2).

In this patient cohort, 4 patients received EBT: 2 (16.67 %) in the pazopanib → sorafenib group and 2 (8.00 %) in the pazopanib → sunitinib group (see Table 3). As part of therapy, in advisable cases we also sought to perform metastasectomies and surgeries to improve quality of life. Types of surgical interventions performed in patients receiving pazopanib → sorafenib and pazopanib → sunitinib targeted therapies are presented in Table. 4. Estimation of cPFS for the pazopanib → sorafenib and pazopanib → sunitinib sequential therapy lines in patients with mRCC is presented in Figure 3.

We also compared pazopanib → sunitinib (n = 25) and sunitinib → pazopanib (n = 32) therapies. Estimation of cPFS for these therapies is presented in Figure 4. Comparison between cPFS in the pazopanib → sorafenib and sorafenib → pazopanib groups is presented in Figure 5.

Conclusion

Currently, there are several studies of sequential targeted therapies: evaluation of effectiveness of sorafenib administration with subsequent sunitinib administration, and vice versa, and effectiveness of sorafenib and sunitinib as the 1st line therapies with subsequent prescription of pazopanib.

We analyzed the main retrospective studies and randomized clinical trials of sequential targeted therapy.

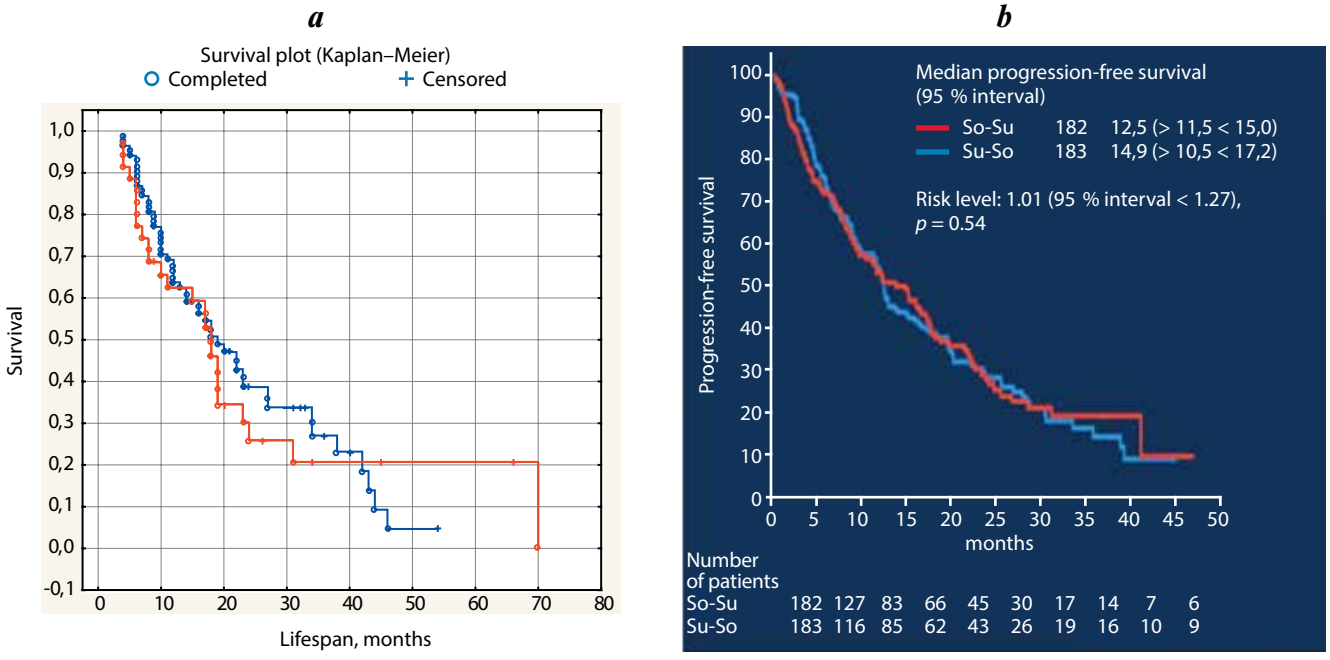

Fig. 1. *Comparison of cumulative progression-free survival for administration of targeted drugs in the sorafenib → sunitinib and sunitinib → sorafenib sequential targeted therapy lines in metastatic renal cell carcinoma: a – current study; b – SWITCH study (So – sorafenib; Su – sunitinib)*

Table 2. *Characteristics of the patient groups receiving sequential therapy with tyrosine kinase inhibitors*

Показатель	Sorafenib → sunitinib		Sunitinib → sorafenib		Sunitinib → pazopanib	Pazopanib → sunitinib	Sorafenib → pazopanib	Pazopanib → sorafenib
	V.I. Shirokorad	SWITCH, M.S. Michel et al.	V.I. Shirokorad	SWITCH, M.S. Michel et al.	V.I. Shirokorad	V.I. Shirokorad	V.I. Shirokorad	V.I. Shirokorad
Number of patients, *n*	85	182	35	183	32	25	31	12
Mean age, years (range)	60.68 (29–78)	64 (39–84)	58.88 (43–75)	65 (40–83)	60.40 (46–76)	57.91 (32–68)	61.50 (40–83)	57.91 (32–68)
Women, *n* (%)	20 (23.52)	n/д (23.6)	9 (25.71)	n/a (26.2)	7 (21.88)	5 (41.67)	9 (29.00)	5 (41.67)
Men, *n* (%)	65 (76.48)	n/a (76.4)	26 (74.29)	n/a (73.8)	25 (78.13)	7 (58.33)	22 (70.97)	7 (58.33)
Affected side, *n* (%): right left both kidneys	 44 (51.76) 39 (46.88) 2 (2.36)		 13 (37.10) 20 (57.14) 2 (5.72)		 14 (43.76) 18 (56.25) 0	 6 (50.00) 6 (50.00) 0	 16 (51.61) 14 (45.16) 1 (3.23)	 6 (50.00) 6 (50.00) 0
Surgery type, *n* (%): nephrectomy kidney resection other	 78 (91.77) 2 (2.36) 5 (5.87)	n/a (91.8)	 30 (85.71) 4 (11.43) 1 (2.86)	n/a (91.8)	 29 (90.63) 2 (6.25) 1 (3.13)	 10 (83.33) 0 0	 29 (93.55) 0 2 (6.45)	 1 0 (83.33) 0 0
ECOG performance status, *n* (%): 0 1 2 3 not determined	 1 (1.18) 3 (3.53) 10 (11.76) 3 (3.53) 68 (80.00)	 n/a (67.8) n/a (32.2)	 0 2 (5.71) 1 (2.86) 2 (5.71) 30 (8.57)	 n/a (61.3) n/a (38.2)				
MSKCC risk group, *n* (%): favorable intermediate poor not determined	 2 (2.35) 11 (12.94) 4 (4.70) 68 (80.00)	 n/a (39.0) n/a (59.3) n/a (0.5) –	 – – 3 (8.57) 2 (5.71) 30 (8.57)	 n/a (44.8) n/a (51.4) n/a (0.5) –				
Morphological variant of the tumor, *n* (%): clear cell papillary chromophobe sarcoma-like collecting duct mixed	 82 (96.47) 2 (2.36) 0 1 (1.17) 1 (1.17) 0	n/a (90.1)	 33 (94.29) 2 (5.71) 0 0 0 0	n/a (84.2)	 32 (100.00) 0 0 0 0 0	 19 (76.00) 1 (4.00) 0 1 (4.00) 0 0	 29 (93.55) 1 (3.23) 0 1 (3.23) 0 0	 11 (91.67) 0 0 1 (8.33) 0 0
Metastases localization, *n* (%): lungs bones brain liver lymph nodes adrenal gland	 23 (27.10) 9 (10.60) 2 (2.36) 4 (4.70) 7 (8.24) 4 (4.70)		 26 (74.29) 7 (20.00) 2 (5.71) 4 (11.43) 15 (42.86) 6 (17.14)		 18 (56.25) 9 (28.13) 3 (9.38) 3 (9.38) 10 (31.25) 5 (15.63)	 16 (64.00) 9 (36.00) 3 (12.00) 2 (8.00) 4 (16.00) 4 (16.00)	 19 (61.29) 11 (35.48) 2 (6.45) 3 (9.68) 9 (29.00) 0	 7 (58.33) 4 (33.33) 0 0 0 0
Beam therapy, *n* (%)	9 (10.59)		4 (11.43)		4 (12.50)	2 (8.00)	3 (9.67)	2 (16.67)
Stereotaxy (Gamma Knife for brain metastases), *n* (%)	2 (2.35)		4 (11.43)		1 (3.13)	0	2 (6.45)	0

Note. *n/a – data not available.*

Table 3. *Characteristics of the patient groups receiving external beam therapy in combination with targeted therapy*

Irradiated area	Dose, Gy					
	sorafenib → sunitinib	**sunitinib → sorafenib**	**sunitinib → pazopanib**	**pazopanib → sunitinib**	**sorafenib → pazopanib**	**pazopanib → sorafenib**
EBT of metastases in the C7 vertebra	SD – 2 CD – 36					
EBT of metastases in the L1 vertebra	CD – 32					
EBT of metastases in the L2 vertebra	CD – 28		CD – 30			
EBT of metastases in the L4 vertebra	CD – 25					
EBT of metastases in the Th10 vertebra	CD – 32					
EBT of a destruction lesion in the rib X on the right	SD – 3 CD – 42					
EBT of recurrence in the right cerebellar hemisphere	CD – 54					
EBT of osteolytic metastasis in the right tibia	CD – 24					
EBT of the removed left kidney fossa	CD – 44	CD – 48			CD – 40	
EBT of the removed right kidney fossa	CD – 40	CD – 40			SD – 2 CD – 60	
EBT of metastases in the C3 vertebra		CD – 24	CD – 36			
EBT of the ilium		SD – 5 CD – 20	CD – 32	CD – 40		CD – 49
EBT of the right side of the sacral bone with sacroiliac joint					SD – 5 CD – 40	
EBT of the lesser and greater femur trochanter from 2 opposed fields					SD – 5 CD – 40	
EBT of the right pelvis, right sacroiliac joint and upper third of the right femur			CD – 30			
EBT of metastases in the Th6 vertebra with adjoining dorsal part of the rib VI						CD – 45
EBT of metastases in the Th12 vertebra				CD – 54		
Total number of patients, n (%)	*9 (10.59)*	*4 (11.43)*	*4 (12.50)*	*2 (8.0)*	*3 (9.67)*	*2 (16.67)*

Note. *EBT – external beam therapy; SD – single dose; CD – cumulative dose.*

We consider SWITCH and SWITCH II the most important of them [8]. Results of these studies are presented in Table 5.

Thus, results of our retrospective analysis are similar to final results of many other retrospective studies, including the SWITCH multicenter randomized study. We haven't observed any principal differences between the sorafenib → sunitinib and sunitinib → sorafenib sequential targeted therapies considering that cPFS in the 2 sequential therapies using tyrosine kinases (16.9 and 18.2 months, respectively) were almost equal.

There's no statistically significant difference between the preliminary results of the SWITCH II multicenter randomized study and our results on cPFS for administration of tyrosine kinase inhibitors (sorafenib and sunitinib) as the 1st line therapy with subsequent administration of pazopanib as the 2nd line therapy (12.5 and 14.4 months, respectively) and pazopanib as the 1st line therapy with tyrosine kinase inhibitors (sorafenib and sunitinib) as the 2nd line therapy (12.5 and 11.56 months, respectively).

We support aggressive tactics of metastases treatment during targeted therapy, as we have shown in this study.

Table 4. *Types of surgeries performed in patients receiving sequential targeted therapy*

Surgery	Sorafenib → sunitinib	Sunitinib → sorafenib	Sunitinib → pazopanib	Pazopanib → sunitinib	Sorafenib → pazopanib	Pazopanib → sorafenib
Metastasectomies						
Lung resection	4	7	4	1	3	
Lobectomy	2	1				
Maxillectomy	1					
Right breast resection	1					
Removal of tumors of soft tissues	1				1	
Right shoulder blade resection	1					
Femur resection with knee joint endoprosthesis	1	1				
Resection of Th11 vertebra metastases with Th10 – Th12 stabilization	1					
Amputation of the left femur due to pathological fracture	1					
Resection of the proximal area of the right humerus with endoprosthesis	1					
Clavicle resection	1					
Resection of the L4 body with metal implant installation	1					
Removal of sacral bone metastases	1					
Removal of scalp metastases	1		1			
Removal of brain metastases	5	1	1	2	1	
Removal of parotid salivary gland metastases	1					
Removal of urethral metastases	1					
Thrombectomy, inferior vena cava resection	1					
Strumectomy due to thyroid metastases	1					
Resection of the solitary right kidney, pancreatectomy, cholecystectomy, splenectomy, duodenectomy with stomach resection, right adrenalectomy		1				
Resection of soft tissue tumor and lymph nodes of the right axilla		1				
Adrenalectomy		2	1			2
Retroperitoneal lymph node dissection, removal of recurrent tumor		1		1	2	
Removal of recurrence in the right kidney, removal of the 7th liver segment, cholecystectomy				1		
Left hemicolectomy					1	
Liver resection					1	
Spondylectomy of C3, transpedicular L1–L3 vertebra stabilization			1			
Metastasectomies						
Distal pancreas resection, splenectomy, adrenalectomy, resection of the solitary right kidney						
Total, n (%)	*27 (31.70)*	*15 (42.90)*	*9 (28.10)*	*5 (2.00)*	*9 (29.03)*	*2 (16.67)*

End of table 4

Surgery	Sorafenib → sunitinib	Sunitinib → sorafenib	Sunitinib → pazopanib	Pazopanib → sunitinib	Sorafenib → pazopanib	Pazopanib → sorafenib
Symptom-oriented surgeries (without removal of metastases)						
Osteoplastic surgery of the left ilium and femurs		1				
Osteosynthesis of the right femur	1					
Decompressive laminectomy	1	1	1		1	2
Transcutaneous vertebroplasty	2				1	
Sacroiliac joint prosthesis			2			
Total, n (%)	*4 (4.70)*	*2 (5.70)*	*3 (9.40)*	*0*	*2 (6.45)*	*2 (16.67)*
Grand total, n (%)	***31 (36.47)***	***17 (48.57)***	***12 (37.50)***	***5 (20.00)***	***11 (35.48)***	***4 (33.30)***

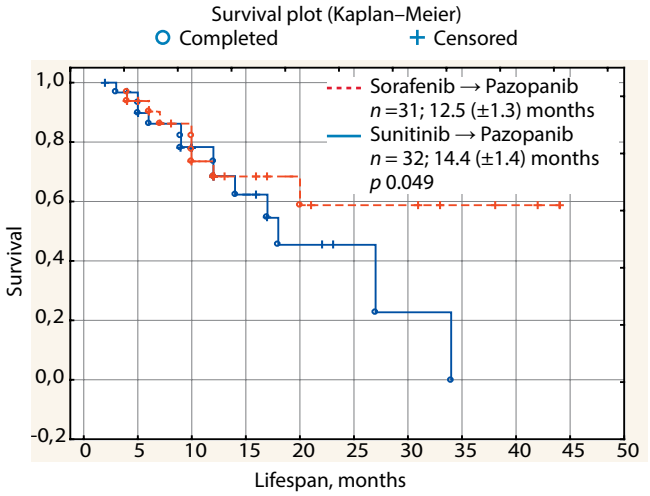

Fig. 2. *Cumulative progression-free survival for administration of targeted drugs in the sorafenib → pazopanib and sunitinib → pazopanib sequential targeted therapy lines in metastatic renal cell carcinoma*

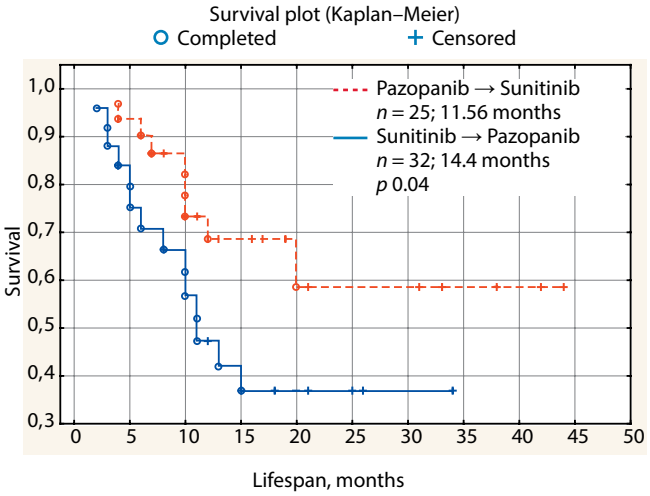

Fig. 4. *Estimation of cumulative progression-free survival time for the pazopanib → sunitinib and sunitinib → pazopanib sequential targeted therapy lines in metastatic renal cell carcinoma*

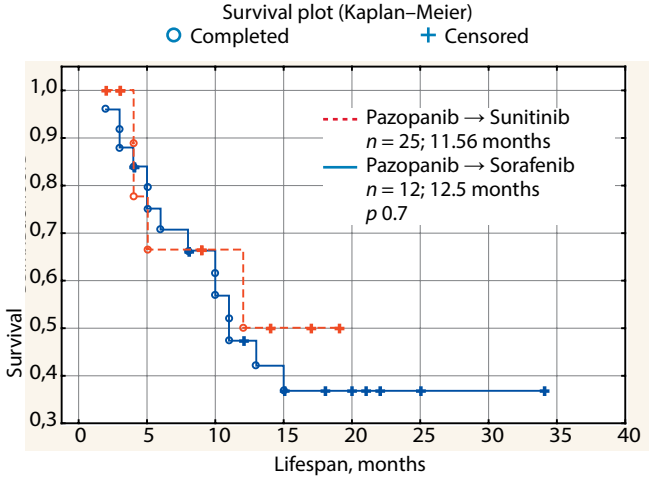

Fig. 3. *Estimation of cumulative progression-free survival for administration of targeted drugs in the pazopanib → sorafenib u pazopanib → sunitinib sequential targeted therapy lines in metastatic renal cell carcinoma*

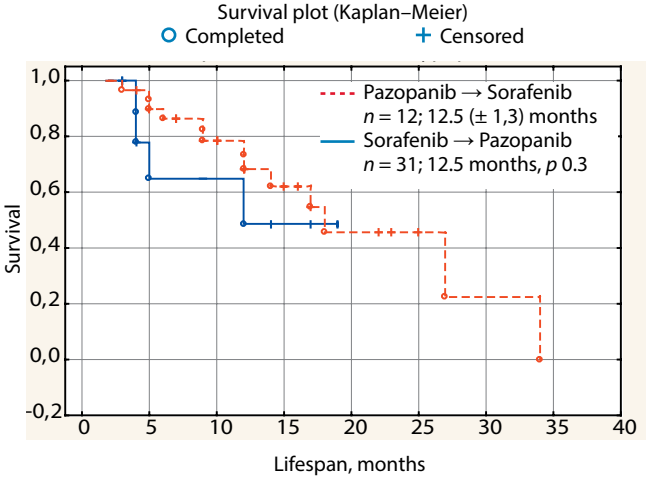

Fig. 5. *Estimation of cumulative progression-free survival time for the pazopanib → sorafenib and sorafenib → pazopanib sequential targeted therapy lines in metastatic renal cell carcinoma*

Table 5. *Retrospective studies and randomized clinical trials of sorafenib → sunitinib and sunitinib → sorafenib sequential therapies in 2009–2016*

Author	Year of publication	Sorafenib → sunitinib				Sunitinib → sorafenib			
		Number of patients, *n*	Progression-free survival, months	Overall survival, months	Significance (*p*), risk ratio (RR)	Number of patients, *n*	Progression-free survival, months	Overall survival, months	Significance (*p*), risk ratio (RR)
V.I. Shirokorad	2016	85	16.9	–	$p = 0.047$	35	18.2	–	–
M.S. Michel et al., SWITCH, phase III [8]	2014	182	12.5	31.5	$p = 0.92$ RR 1.19	183	14.9	30.2	$p = 0.49$ RR 0.997
M.P. Sablin et al. (retrospective) [9]	2009	68	12.4	31.5	–	22	9.0	19.1	$p = 0.04$ RR 0.49
A.Z. Dudek et al. (retrospective) [10]	2009	29	18.2	23.8	$p = 0.016$ RR 3.0	20	8.5	10.5	$p = 0.061$
E. Herrmann et al. [11]	2011	33	12.1	28.8	–	54	15.4	28.8	–
T. Buchler et al. [12]	2012	122	18.8	30.0	$p = 0.47$ RR 1.1	138	17.7	35.4	$p = 0.99$ RR 0.9
C. Porta et al. (retrospective) [13]	2011	90	16.3	–	–	99	12.0	–	–
F. Stenner et al. [14]	2012	455	15.3	–	$p = 0.003$	405	12.4	–	$p = 0.0013$
G. Di Lorenzo et al. [15, 16]	2009	–	–	–	–	52	3.7	7.4	–
S.-T. Wang et al. [17]	2009	53	10.0	–	–	28	10.1	–	–
T.K. Choueiri et al. (retrospective) [18]	2008	31	13.4	–	–	7	21.0	–	–
I. Tamaskar et al. (retrospective) [19]	2008	4	12.1	–	–	5	14.5	–	–
S. Richter et al. (retrospective) [20]	2009	5	17.7	–	–	5	17.5	–	–
K. Zimmermann et al. (retrospective) [21]	2009	22	16.6	–	–	–	–	–	–
C. Eichelberg et al. (retrospective) [22]	2009	30	17.3	–	–	–	–	–	–

Only combination therapy allows to achieve the longest progression free-survival times possible, as well as improve quality of life of patients with mRCC. Sequential treatment with tyrosine kinase inhibitors doesn't rule out 2nd and subsequent therapy lines with targeted drugs from other groups.

Therefore, we consider prescription of targeted drugs in sequential therapy an important process requiring serious consideration and comparison of all parameters characterizing metastatic process and functional state of the patient's body.

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