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The use of targeted therapies and selection of the optimal treatment sequence in heterogeneous population of patients with metastatic kidney cancer. Results of retrospective study

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Renal cancer is one of the most rapidly spreading diseases in the world. As you know, a few years ago, overall survival of patients with metastatic renal cell carcinoma (mRCC) was disappointing: median overall survival rarely exceeded 13 months, while 5-year survival rate was less than 5 %. Immunotherapy with interferon-alpha and interleukins demonstrated low efficiency. Appearance of targeted therapies for the treatment of mRCC significantly increased the duration and quality of life of patients receiving drug treatment. Nowadays due to this methodology and guided by the results of randomized clinical trials we can choose an optimal sequence of therapy and control the disease in three consecutive lines for about 30 months. In this article we would like to share an experience of the use of targeted therapies in the Saint Petersburg City Clinical Oncology Dispensary in patients with clear-cell mRCC.

Key words: *metastatic renal cell cancer, targeted medications, progression-free survival, overall survival*

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Introduction

Renal cancer is one of the most rapidly spreading diseases in the world [1]. In the last quarter of the century, morbidity of localized forms increased almost twofold: from 7.6 to 12.2 per 100,000 people; morbidity of locally advanced and metastatic renal cancer remains roughly the same: 3 per 100,000 people.

In Russia in 2012, 8,265 cases of renal cell carcinoma (RCC) were registered, but in 2013 there already were 10,841 cases [2]. Morbidity is 12.9 per 100,000 people. In about 25 % of patients [3] kidney cancer is diagnosed at the stage of locally advanced or metastatic process, and in about a quarter of patients, progression in the form of distant metastases is observed. Mortality rate of renal cancer is 5.2 %. Mean patient age is 61.6 years. In Russia, morbidity increases while mortality remains constant. In Saint-Petersburg in 2014, 220 patients with renal cancer were registered (Medical Information and Analysis Center's data).

Even several years earlier, overall survival (OS) of patients with metastatic RCC (mRCC) was disappointing: Median OS rarely exceeded 13 months, and 5-year survival was less than 5 % [4]. Immunotherapy (IMT) with interferon alfa (INF) drugs and interleukins showed low effectiveness. Some authors have demonstrated a modest benefit of cytokine therapy compared to placebo [5, 6]. In patients with intermediate risk per MSKCC (Memorial Sloan-Kettering Cancer Center), there were no advantages of cytokine treatment compared to placebo [7]. Development of targeted drugs to treat mRCC lead to a significant increase in the duration and quality of life of patients receiving drug treatment. The advent of sorafenib in 2005 marked a new era of mRCC treatment. Today, using this treatment methodology and following the results of randomized clinical trials, we can choose an optimal therapy sequence and control disease progression for about 30 months. Every targeted drug is optimal for mRCC patients with specific characteristics considering the previous line drug. Selection of the optimal tactics is based on patient stratification by risk which was developed in the era of cytokines using the MSKCC prognostic model. Using risk factors included in the model, 3 prognosis groups were established: favorable, intermediate, and poor [8]. Ability to choose a drug for targeted therapy based on the prognosis group allowed to create optimal patient cohorts for the best response to treatment possible. Obviously, patient groups receiving targeted therapy in randomized studies differ from the general population of mRCC patients, and doctors are interested in the effectiveness, tolerability, and advisability of these drugs for a specific patient with mRCC [9].

In this article, we would like to share our experience of using targeted drugs to treat patients with clear cell mRCC at the Saint Petersburg City Clinical Oncology Dispensary.

Materials and methods

We analyzed data of 147 patients receiving treatment for mRCC at the Saint-Petersburg City Clinical Oncologi-

cal Dispensary and the Russian Scientific Center of Radiology and Surgical Technologies in 2008–2015. All patients were receiving at least 1 line of targeted therapy for 3 months. Mean age of patients included in the study was 61.7 (28–82) years. The disease developed in men twice as often as in women. The main patient characteristics are presented in Table 1. In all patients, histological examination of the primary tumor revealed clear cell RCC.

Severity of the disease and localization of metastases are presented in Table 2.

Treatment was prescribed in accordance with general oncological principles. All patients were transferred to the next therapy line after progression. Thus, all 147 (100 %) patients received the 1st line of treatment, 80 (54.4 %) received the 2nd line, 20 (13.6 %) – the 3rd, 4 (2.7 %) and 3 (2.0 %) – the 4th and the 5th, respectively (Table 3).

The primary endpoint was median time to progression (TTP). Secondary endpoints were medial OS in the 1st, 2nd, and 3rd therapy lines and overall response rate (OR + stabilization) and objective response rate (OR = CR + PR). The Kaplan-Meier estimator was used for survival plots, differences in survival were compared using the log-rank test. Statistically significant were differences with the significance level $p < 0.05$. Mathematical processing of the results was performed using the Statistica and MedCalc 15.6.1 software.

Table 1. *Main patient characteristics and types of surgical interventions*

Characteristic	Value	%	p
Age (range), years	61.7 (28–82)		
Men	98	66.7	0.028
Women	49	33.3	0.028
Radical nephrectomy	99	67.3	0.78
Cytoreductive nephrectomy	48	32.7	0.78
Partial cytoreduction	47	32.0	0.09
Relapse-free period (range), months	38.5 (1–187)		

Table 2. *Characteristics of patients with metastatic renal cell carcinoma with the respect to disease severity*

Characteristic	Subgroup	Total.	%	p
Prognosis per MSKCC	Total Favorable Intermediate Poor	147 30 85 32	100 20.4 57.8 21.8	0.07
ECOG performance status	Total 0 1 2	147 31 86 30	100 21.1 58.5 20.4	0.48
Number of affected organs	Total 1 2 3 4 and more	147 54 44 30 19	100 36.7 29.9 20.4 12.9	0.098
Maximum number of metastases in 1 organ	Total 1 $1 < n < 3$ > 3	147 34 37 76	100 23.1 25.2 51.7	0.42
Localization of metastatic lesions before the 1st therapy line	Total Lungs Regional lymph nodes Recurrence in the fossa Contralateral kidney Distant lymph nodes Liver Adrenal gland Bones Brain Other location (thyroid gland, ovary, skin)	147 103 26 26 17 33 20 21 41 7 19	100 70.1 17.6 17.6 11.6 22.4 13.6 14.3 27.9 4.8 12.9	0.09 0.1 0.92 0.17 0.6 0.42 0.1 0.06 0.5 – 0.0007

Table 3. *Main characteristics of types of systemic treatment in patients with metastatic renal cell carcinoma in respect to therapy line*

Therapy line	Subgroup	Total	%	p
1st	Total Interferon alfa Bevacizumab + interferon alfa Pazopanib Sorafenib Sunitinib	147 55 10 12 42 28	100 37.4 6.8 8.2 28.6 19.0	0.008
2nd	Total Interferon alfa Bevacizumab + Interferon alfa Pazopanib Sorafenib Sunitinib Axitinib Everolimus	80 1 1 4 27 21 11 15	100 1.3 1.3 5.0 33.8 26.3 13.8 18.8	
3rd	Total Pazopanib Sorafenib Sunitinib Everolimus	20 5 4 4 7	100 25.0 20.0 20.0 35.0	
4th	Total Pazopanib Sorafenib Sunitinib	4 1 2 1	100 25.0 50.0 25.0	
5th	Total Sunitinib Everolimus	3 1 2	100 33.3 66.7	

Results

Mean treatment duration was 28.0 (4.0–30.9) months. Effectiveness and overall response rate for the drugs and therapy lines are presented in Table 4.

Only for sunitinib full remission was observed in 2 patients. Apart from that, sunitinib (25.0 %) and bevacizumab (30.0 %) demonstrated the highest objective response rate. The lowest objective response rate was in patients receiving IMT (9.1 %). In every 3rd patient receiving IMT (29.1 %), maximum response to treatment was progression, while for other drugs it didn't exceed 11.2 %. Nonetheless, overall response rate for IMT was 70.9 %. In 8 patients, long-term stabilization (longer than 5 years) was observed.

More than a half of patients (54.5 %) who received the 1st line therapy, received the 2nd line after progression. The following drugs were used to treat mRCC: sorafenib (n = 27), sunitinib (n = 21), everolimus (n = 18), and axitinib (n = 11). The highest objective response rate (ORR) was in the axitinib and sorafenib groups: 18.2 and 14.9 %, respectively. ORR for everolimus was 6.7 %. No objective responses were reported for sunitinib. The highest progression rate was observed for sunitinib (28.6 %), while sorafenib and everolimus didn't reach the threshold of 15.0 %, and axitinib didn't have any (see Table 4).

The 3rd line was prescribed to 20 patients. It consisted of everolimus, pazopanib, sorafenib, or sunitinib: 7, 5, 4, and 4 patients, respectively. In 14 (70 %) cases stabilization was achieved, and in 6 (30 %) cases progression was observed.

Table 4 also includes data on patients who received the 4th therapy line and 3 patients who received the 5th.

To evaluate median TTP and median OS in the 1st therapy line we studied 3 drugs with the largest samples: interferon 2β (n = 55), sorafenib (n = 42), and sunitinib (n = 28). Median TTP was 11 months (95 % confidence interval (CI) 8–12). Treatment duration was 1–62 months. Targeted therapy demonstrated statistically significant superiority in TTP ($p < 0.0001$) above IMT: 14 months (95 % CI 10–21) and 12 months (95 % CI 10–16) for sunitinib and sorafenib, respectively, compared to 7 months (95 % CI 5–9) for IMT (Fig. 1).

Median OS was the highest in the sunitinib group: 37.4 months (95 % CI 28.6–46.2). In the INF and sorafenib groups this value was 37.2 months (95 % CI 31.6–42.7) and 29.0 months (95 % CI 23.3–36.0), respectively. The significance level wasn't reached (p = 0.43) (Fig. 2).

Evaluation of medial TTP showed benefits of axitinib compared to the other studied drugs (Fig. 3). TTP for axitinib was 16 months (95 % CI 6–18). Sorafenib showed

Table 4. *Main characteristics of the received systemic treatment in patients with metastatic renal cell carcinoma*

Drug	Total, abs. (%)	Complete response + partial response, abs. (%)	Stabilization, abs. (%)	Progression, abs. (%)
1st line, n = 147				
Immunotherapy	55 (37.4)	5 (9.1)	34 (61.8)	16 (29.1)
Bevacizumab + interferon	10 (6.8)	3 (30.0)	7 (70.0)	–
Pazopanib	12 (8.2)	2 (16.7)	9 (75.0)	1 (8.3)
Sorafenib	42 (28.6)	8 (19.4)	29 (69.0)	5 (11.2)
Sunitinibб	28 (19.0)	7 (2/5) (25.0)	20 (71.4)	1 (3.6)
2nd line, n = 80				
Immunotherapy	1 (1.3)	– –	1 (100.0)	–
Bevacizumab + interferon	1 (1.3)	1 (25.0)	1 (100.0)	–
Pazopanib	4 (5.0)	4 (14.9)	3 (75.0)	–
Sorafenib	27 (33.8)	–	19 (70.2)	4 (14.9)
Sunitinib	21 (26.3)	2 (18.2)	15 (71.4)	6 (28.6)
Axitinib	11 (13.8)	1 (6.7)	9 (81.8)	–
Everolimus	15 (18.8)	–	12 (80.0)	2 (13.3)
3rd line, n = 20				
Pazopanib	5 (25.0)	–	3 (60.0)	2 (40.0)
Sorafenib	4 (20.0)	–	3 (75.0)	1 (25.0)
Sunitinib	4 (20.0)	–	4 (100.0)	–
Everolimus	7 (35.0)	–	4 (57.1)	3 (42.9)
4th line, n = 4				
Pazopanib	1 (25.0)	–	1 (100.0)	–
Sorafenib	2 (50.0)	–	1 (50.0)	1 (50.0)
Sunitinib	1 (25.0)	–	–	1 (50.0)
5th line, n = 3				
Sunitinib	1 (33.4)	–	–	1 (100.0)
Everolimus	2 (66.7)	–	1 (50.0)	1 (50.0)

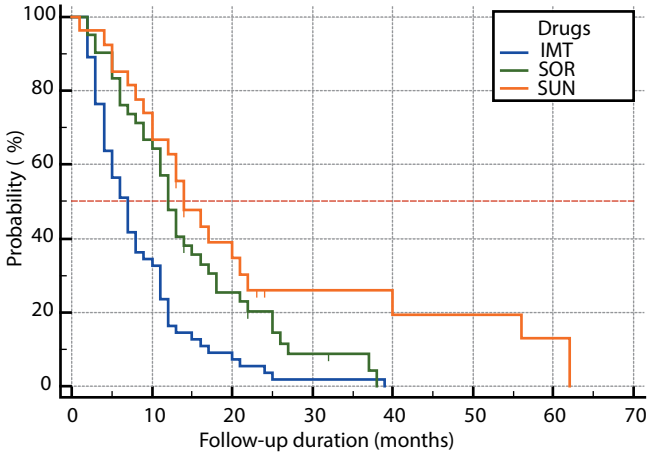

Рис. 1. *Fig. 1. Median progression-free survival in treatment of metastatic renal cell carcinoma in the 1st line of systemic therapy. Effectiveness of targeted therapy compared to immunotherapy. Here and in Fig. 2–4: AXI – axitinib, IMT – immunotherapy, SOR – sorafenib, SUN – sunitinib, EVE– everolimus*

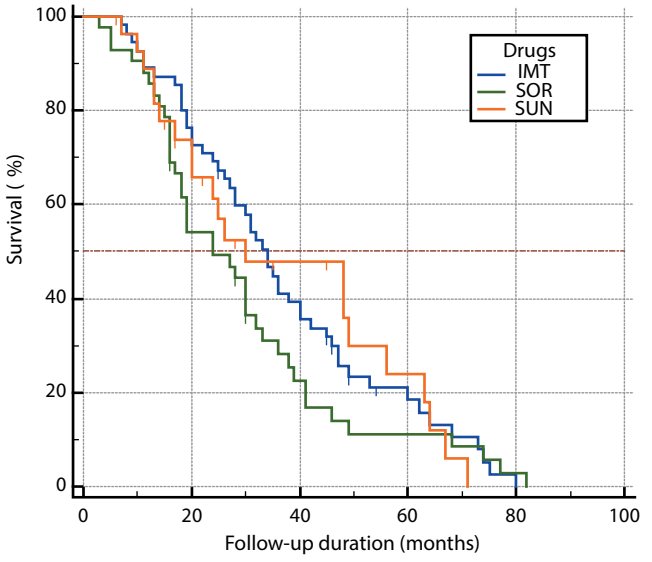

Fig. 2. *Overall survival in respect to the choice of the 1st line dru*

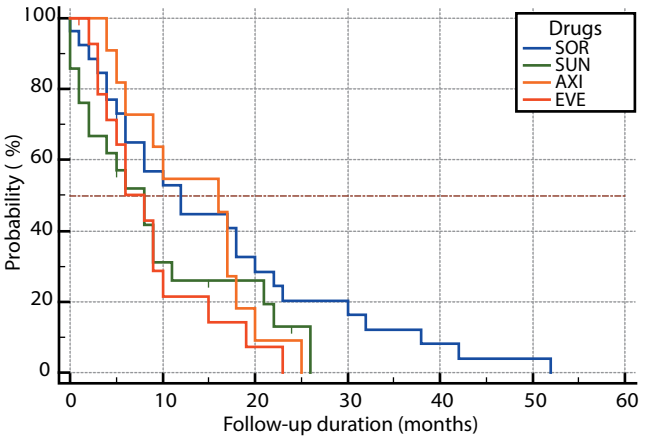

Fig. 3. *Time to progression in the 2nd line of systemic treatment of metastatic renal cell carcinoma in respect to the drug of choice*

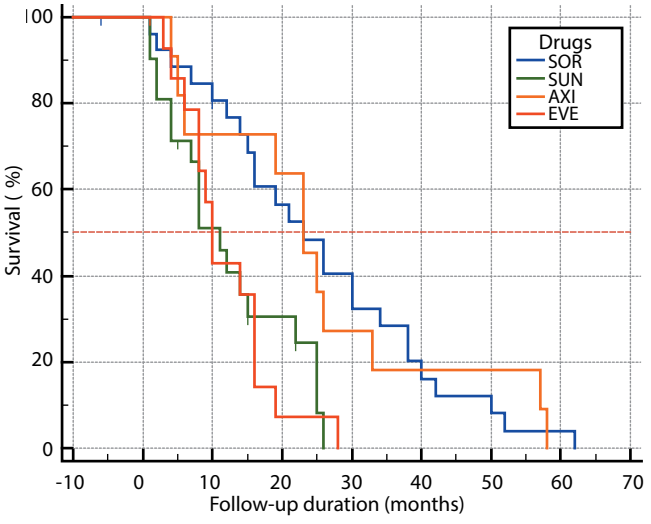

Fig. 4. *Overall survival for the 2nd line of systemic treatment in patients with metastatic renal cell carcinoma (p = 0.008)*

a little lower duration of treatment effect: 12 months (95 % CI 6–20). Sunitinib and everolimus were significantly worse in this regard: 8 and 6 months, respectively. Significance level for TTP in the 2nd therapy line wasn't reached ($p = 0.14$).

Median OS for the 2nd therapy line also demonstrated superiority of axitinib and sorafenib: 25.3 months in both groups (95 % CI 18.9–31.6 and 14.4–36.2, respectively). For sunitinib and everolimus OS was 12.4 and 11.9 months, respectively (95 % CI 8.4–16.5 and 8.4–15.4, respectively). However, unlike median TTP, differences in median OS were statistically significant ($p = 0.008$) (Fig. 4).

The 3rd therapy line included 20 patients with mRCC: 7 (35 %) received everolimus, the rest 13 (65 %) were prescribed tyrosine kinase inhibitors (pazopanib, sorafenib, sunitinib). Median TTP was 5 months (95 % CI 2–6) (Fig. 5a). In the 3rd therapy line median OS for all targeted drugs was 8 months (95 % CI 5–14) (Fig. 5b).

Conclusion

Analysis of the study results show that effectiveness of treatment of patients receiving targeted therapy in all lines doesn't significantly differ from the results of randomized clinical trials. Targeted therapy demonstrated significantly higher TTP ($p < 0.0001$) compared to IMT: TTP in patients in the sunitinib and sorafenib groups reached 14 and 12 months, respectively, while in the IMT group it was only 7 months. No significant differences in OS were observed for the 1st line drugs. ORR in patients receiving sunitinib was a little higher than in other groups: 25 %, and in 2 cases full remission was observed. Twofold difference between sunitinib and IMT was expected; nonetheless, 3/4 of patients receiving IMT responded to treatment, and in every 10th patient partial remission was observed.

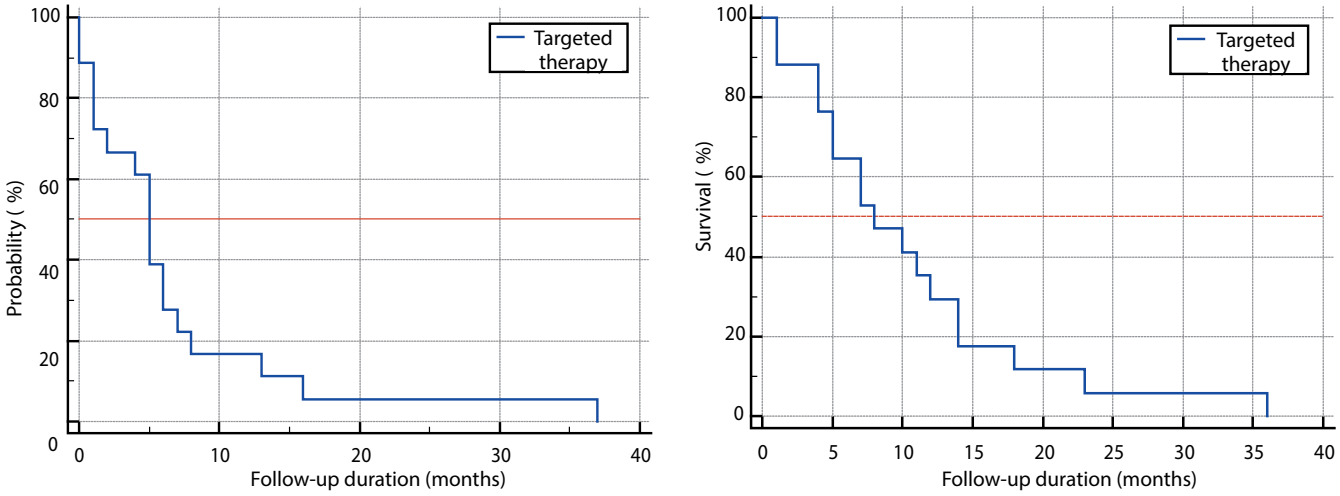

Fig. 5. *Progression-free survival (a) and overall survival (b) in the 3rd line of systemic therapy of metastatic renal cell carcinoma*

The use of everolimus as the 2nd line drug lately has been questioned, and our study confirms inadvisability of this choice. The drugs of choice in this line are sorafenib and axitinib which showed high median TTP and OS; the results were statistically significant.

Due to small sample size, we couldn't determine the optimal drug for the 3rd therapy line. However, response to treatment was observed in the form of median TTP of 5 months. The use of targeted drugs in the 4th and 5th therapy lines suggests enormous hidden potential in treatment of mRCC.

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