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Optimization of sequential targeted therapy

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Renal cell carcinoma (RCC) takes one of the leading places in the world incidence among malignant tumors of the genitourinary system. Metastatic renal cell cancer (mRCC) is detected in about 25–30 % of primary patients. 10 targeted immuno-oncology drugs for the treatment of mRCC were registered and approved for use from 2005 till the present time. Rapid growth of therapeutic options of mRCC treatment has created a problem for practicing oncologists and urologists as well as necessity to understand the principles and consistent optimization of targeted therapy to maximize the effectiveness of each treatment line. The article discusses issues of the correct choice of first-line targeted drugs, optimal dosing of sunitinib and axitinib, alternative modes and alternating use of sunitinib, as well as the influence of objective response and hypertension, which developed on the background of the targeted therapy on the effectiveness of treatment.

Key words: *metastatic renal cell carcinoma, targeted therapy, tyrosine kinase inhibitors, sunitinib, axitinib*

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Renal cell carcinoma (RCC) is one of the most common malignant tumors of the urogenital system. In 2012, more than 337,000 patients with primary RCC were registered worldwide, 143,369 patients died from RCC [1]. In Russia in 2014, 22,234 new cases of RCC were registered. This corresponds to 3.92 % of the total cancer morbidity. Morbidity increase rate for RCC has been one of the largest in the last ten years (29.39 %). Total number of lethalities in Russia in 2014 was 8,430 people, but in the last 3 years mortality decreased by 7.08 % which supposedly is a result of earlier diagnosis and improvement of treatment of late stages [2].

In recent years, research of molecular mechanisms of tumor growth and progression in patients with RCC stimulated development of a new treatment approach in oncological urology – targeted therapy. Since 2005 and to date 10 targeted and immuno-oncological drugs were registered and approved for treatment of metastatic RCC (mRCC): sorafenib (Nexavar®); sunitinib (Sutent®); bevacizumab (Avastin®) in combination with interferon alfa; pazopanib (Votrient®); temsirolimus (Torizel®); axitinib (Inlyta®); everolimus (Afinitor®); cabozantinib (Cabometyx®); lenvatinib (Lenvima®) in combination with everolimus and nivolumab (Opdivo®). Treatment with targeted drugs gave unique results: increase in relapse-free survival and overall survival (OS) of mRCC patients accompanied by moderate toxicity of the drugs which allows to conduct therapy on the out-patient basis. All drugs approved after 2013 are used in the 2nd or subsequent lines of therapy, while drugs of the 1st line remain unchanged: sunitinib, bevacizumab in combination with interferon alfa, pazopanib. Fast growth of therapeutic options for mRCC treatment created a problem of choice for oncologists and urologists, and a necessity to use optimization of sequential targeted therapy to achieve maximum effectiveness of every line of therapy [3–10].

In contrast to routine chemotherapy with cytostatic drugs administered at certain time periods, treatment with targeted agents is continuous and long-term, in some cases it can take several years. A lengthy break in therapy or its cancellation due to side effects can lead to fast progression of the disease. Therefore, modern and effective therapy of side effects and their prevention are an important part of achieving maximum effectiveness of the treatment and help to avoid unnecessary dose reduction, interruption or cancellation of treatment, and discomfort associated with the therapy [11].

One of the first approved 1st line drugs was sunitinib registered more than 10 years ago. Its effectiveness was proved in several thousands of patients. Sunitinib is a tableted tyrosine kinase inhibitor affecting all known types of PDGF and VEGF, c-KIT and FLT-3 receptors participating in tumor growth, pathological angiogenesis, and metastasis. The most common reported non-hematological side effects in a phase III clinical study of sunitinib were diarrhea, fatigue, nausea, stomatitis, vomiting, hypertension, and palmar-plantar erythrodysesthesia. The most reported hematological side effects were leukopenia, neutropenia, and thrombocytopenia [12, 13].

In order to improve sunitinib»s safety profile, several studies of alternative dosing regimens were conducted. Thus, in a randomized phase II trial, sunitinib dose of 37.5 mg daily didn»t show any advantages compared to traditional dosing regimen of the drug [14].

Another approach to decrease sunitinib toxicity is a change in dosing schedule from a 4/2 (4 weeks on/2 week off) schedule to a 2/1 (2 weeks on/1 week off) schedule. Thus, B. Neri et al. have shown that the 2/1 schedule has better tolerability than the 4/2 schedule [15]. A similar investigation was conducted by T. Kondo et al. who in the period from January 2010 to December 2012 studied 48 patients with mRCC, 26 of whom received sunitinib according to the 2/1 schedule, and 22 – according to the 4/2 schedule. Objective response rate in the 4/2 group was higher than in the 2/1 group (50 % vs. 32 %), and median

progression-free survival (PFS) was higher in the 2/1 group compared to the 4/2 group (18.4 months vs. 9.1 months). However, these results weren't statistically significant ($p = 0.14$; $p = 0.13$). The authors noted that the 2/1 schedule had a lower cancellation rate (27 % vs. 53 %, $p = 0.04$) and initial oncological results compared to the standard 4/2 schedule [16].

Y.G. Najjar et al. analyzed results of treatment of 30 patients with mRCC who received sunitinib as the 1st line targeted therapy and for whom dosing schedule was empirically changed to 2/1. Grade III and IV adverse effects (AEs) were reported for 97 % of patients receiving sunitinib according to the 4/2 schedule. For the 2/1 schedule, there weren»t any grade IV AEs, and grade III AEs were reported in 27 % of patients ($p = 0.0001$). The most common AEs were fatigue and palmar-plantar erythrodysesthesia, which were rarer for the 2/1 schedule compared to the 4/2 schedule ($p = 0.0003$; $p = 0.0004$). Median treatment duration for the 4/2 schedule was 12.6 months, for the 2/1 schedule it was 11.9 months. The authors concluded that administration of sunitinib per the 2/1 schedule significantly increases treatment duration in patients with grade III AEs who previously received the drug according to the 4/2 schedule [17].

B.J. Atkinson et al. published results of treatment of 187 patients with mRCC included in the study from January 2006 to March 2011. If a patient experienced grade III or IV AEs, their sunitinib schedule was changed to 2/1. The control group received sunitinib according to the standard 4/2 schedule; initially, 87 % of patients received sunitinib according to the standard schedule. During the treatment, 53 % of patients continued receiving sunitinib per the standard schedule, 47 % of patients were transferred to the alternate 2/1 dosing schedule. Clinical characteristics of the patients were comparable. AEs requiring schedule change were hypertension (64 %), palmar-plantar erythrodysesthesia (38 %), diarrhea (32 %). Median time to schedule change was 5.6 months, median OS was 17.7 months (95 % confidence interval (CI) 10.8–22.2) for the standard 4/2 schedule, and 33 months (95 % CI 29.3 – median not reached, $p < 0.0001$) for the 2/1 schedule. Adverse factors affecting OS were ECOG performance status, increased lactate dehydrogenase, decreased albumin, unfavorable prognosis per the Heng score, traditional dosing regimen ($p < 0.05$). B.J. Atkinson et al. concluded that sunitinib administered per the alternate schedule can decrease AE rate and increase treatment effectiveness for patients with mRCC [18].

Results of the largest multicenter study were published in 2015. The study conducted by S. Bracarda et al. included 249 mRCC patients receiving sunitinib as the 1st line therapy. A total of 208 patients received sunitinib per the 4/2 schedule and subsequently due to AEs was transferred to the 2/1 schedule; 41 patients received therapy according to the 2/1 schedule from the beginning. Control group consisted of 211 patients receiving sunitinib per the standard 4/2 schedule. The main goal of the study was analysis of sunitinib»s safety profile. Additionally, PFS, OS, and therapy duration were evaluated. In the 4/2 group switched to 2/1, grade III AEs were significantly rarer (decrease from 45.7 % to 8.2 %, $p < 0.001$). Median therapy duration was 28.2 months in the 4/2 → 2/1 group (total time), 7.8 months in the 2/1 group (95 % CI 7.7–23.0), and 9.7 months (95 % CI 8.9–11.7) in the control group. Median PFS was longer in the 4/2 → 2/1 group and constituted 30.2 months (95 % CI 23.2–47.1), in the 2/1 group it was 10.4 months, and in the control group it was 9.7 months. Median OS in the 4/2 → 2/1 group wasn»t reached, in the 2/1 group it was 23.2 months (95 % CI 10.6 – median not reached), and 27.8 months (95 % CI 23.1–35.8) in the control group. Therefore, the authors concluded that mRCC patients switched to the 2/1 sunitinib schedule had less AEs compared to patients on the 4/2 schedule and, subsequently, better tolerability. Application of the 2/1 schedule can be used in clinical practice as an alternative to decreasing the dose for more personalized treatment of mRCC patients with uncontrollable AEs during the standard 4/2 schedule. Use of the 2/1 schedule allows to delay the start of the 2nd line therapy in progression-free patients with low tolerability. Moreover, improved tolerability evolves into increased PFS and allows to keep an increased sunitinib dose. Undoubtedly, confirmation of these results requires prospective studies [19].

There's an active discussion in the literature on the effect of target drugs» concentration on effectiveness and safety of the therapy. In 2009 B.E. Houk et al. published results of pharmacokinetic and pharmacodynamic meta analysis where they evaluated correlation between sunitinib concentration and results of oncological treatment in patients with solid tumors including gastrointestinal solid tumors and mRCC. The study included 639 patients with solid tumors, pharmacokinetic data was available for 443 patients. Sunitinib dose varied from 25 to 150 mg daily. This study included 169 patients with mRCC from 2 trials, and pharmacokinetic data was available for 149 patients receiving 50 mg of sunitinib daily per the 4/2 schedule. The authors noted that in patients with higher plasma sunitinib concentration time to progression was longer, OS was higher, and frequency (but not severity grade) of fatigue was higher than in patients with lower sunitinib and its metabolite plasma concentration. Therefore, this study confirmed advisability of administration of the full 50 mg dose of sunitinib for improvement of clinical results of treatment [20].

In several studies, evaluation of prognostic markers for response to therapy involved demonstration of how objective response affects patient survival. Thus, a retrospective study of 75 patients with mRCC showed that decrease in the primary tumor size by 10 % or more 2 months after the start of treatment decreases risk of death by 74 % ($p = 0.031$) [21].

One of the largest studies concerning correlation between response to therapy and treatment results was con-

ducted by A.M. Molina et al., who used data from 6 trials to include 1059 patients with mRCC receiving sunitinib as the 1st line therapy. They retrospectively evaluated oncological results of early response (< 12 weeks) patients and late response (> 12 weeks) patients and conducted a comparative analysis of patients who responded to sunitinib therapy and patients without response to therapy. Objective response was observed in 398 (38 %) patients, and full response was reported for 12 patients. Response to therapy at weeks 6, 12, 18, and 24 was observed in 26, 61, 79, and 86 % of patients, respectively. Time before objective tumor response was 10.6 weeks. This value was comparable in previously untreated mRCC patients and cytokine-resistant patients. Median duration of response to therapy in patients with early response was 52 weeks, in patients with late response it was 55 weeks. Even though median progression-free survival in the early response group was 13.8 months and in the late response group it was 20.2 months ($p = 0.001$), there were no significant difference in median OS between these groups (37.8 months vs. 40.8 months, $p = 0.144$). Clinical characteristics in two groups were comparable, except for significantly higher rate of lung metastases in the early response group ($p < 0.01$). Median progression-free survival in patients who responded to the treatment was 16.3 months which is significantly longer than in patients who didn't respond to the therapy (5.3 months, see Figure). Median OS was longer in the response group, 40 months, compared to the no-response group where it was 14.5 months ($p < 0.001$). The authors noted that the results of this study demonstrated possibility of an objective and long-term response to sunitinib therapy irrespective of time of its development. This creates conditions for subsequent effective treatment [22].

The problem of selection of the 1st line drug has been widely discussed, because not all patients have time to receive targeted therapy of the 2nd, 3rd and subsequent lines, so the 1st line drug should be chosen with the utmost care. In 2015, J.J. Knox et al. reported final results of one of the studies concerning selection of the optimal sequence of targeted therapy in patients with mRCC. In the RECORD-3 multicenter randomized phase II study, sequential targeted therapy consisting of sunitinib as the 1st line and everolimus as the 2nd line (SUN → EVE) and therapy consisting of everolimus as the 1st line and sunitinib as the 2nd line (EVE → SUN) were compared. From October 2009 to June 2011 the study included 471 patients with mRCC who haven»t previously received systemic therapy. They were randomized 1:1 into an everolimus 10 mg/day therapy group and a sunitinib 50 mg/day per 4/2 schedule group. After progression according to the RECIST criteria, patients were switched to sunitinib and everolimus, correspondingly. The EVE → SUN group included 238 patients, the SUN → EVE group included 233 patients. Majority of patients in both groups (~ 85 %) were diagnosed with clear cell RCC. Patients who stopped 1st line therapy due to disease progression were transferred from everolimus to sunitinib (128 patients – 55 %) and from sunitinib to everolimus (116 patients – 51 %). The main reason for failure to cross-over and refusal of the 2nd line therapy was unfavorable status associated with progression (~ 40 %). Median follow-up time was 3.7 years. Median PFS was 21.1 months in the EVE → SUN group and 25.8 months in the SUN → EVE (risk ratio (RR) 1.2; 95 % CI 0.91–1.59). Median OS was 22.4 months in the EVE → SUN group and 32.0 months in the SUN → EVE group (RR 1.09; 95 % CI 0.87–1.37). Grade III and IV adverse events associated with the drugs occurred in 62 % of patients from the EVE → SUN group and 71 % of patients from the SUN → EVE group. The authors concluded that the results of this study agree with previously reported data, and once again confirm the necessity of following the standard approach to sequential targeted therapy: initial administration of sunitinib with subsequent administration of everolimus after progression [23].

Introduction of targeted drugs significantly improved prognosis for patients with mRCC, but nonetheless median progression-free survival for the 1st line therapy on average doesn»t exceed 11–12 months due to development of drug resistance. Some authors suggest a rotating schedule of target therapy with alternate administration of tyrosine kinases and mTOR inhibitors to combat drug resistance. In particular, in 2015 I.D. Davis et al. published results of the EVERSUN multicenter phase II study of effectiveness and safety of sunitinib in rotation with everolimus. Sunitinib was administered for 12 weeks at the standard dose of 50 mg daily per the 4/2 schedule. Afinitor was also administered at the standard dose of 10 mg daily per the 5/1 schedule (5 weeks on/1 week off) until disease progression or development of grade III and IV AEs. Since September 2010 to August 2012 the study included 55 patients in the favorable risk (16 %) and intermediate risk (84 %) groups. Eighty percent (80 %) of patients received treatment for 14 weeks and longer; 64 % received therapy for < 22 weeks; 78 % for ≥ 22 weeks. Six-month progression-free survival was 53 % (95 % CI 40–66). Objective response was observed in 13 % of patients (95 % CI 4–22). Median follow-up period was 20 months. During the study tumor progression was observed in 47 (86 %) of 55 patients, and 30 (55 %) of 55 patients died. Median PFS was 8 months (95 % CI 5–10), median OS was 17 months (95 % CI 12 – median not reached). Authors concluded that drug administration regimens of the EVERSUN study are possible and safe, but their effectiveness was less than expected. This once again confirmed advisability of using the standard 1st line targeted therapy approaches for as long as possible considering constant effectiveness and satisfactory tolerability [24].

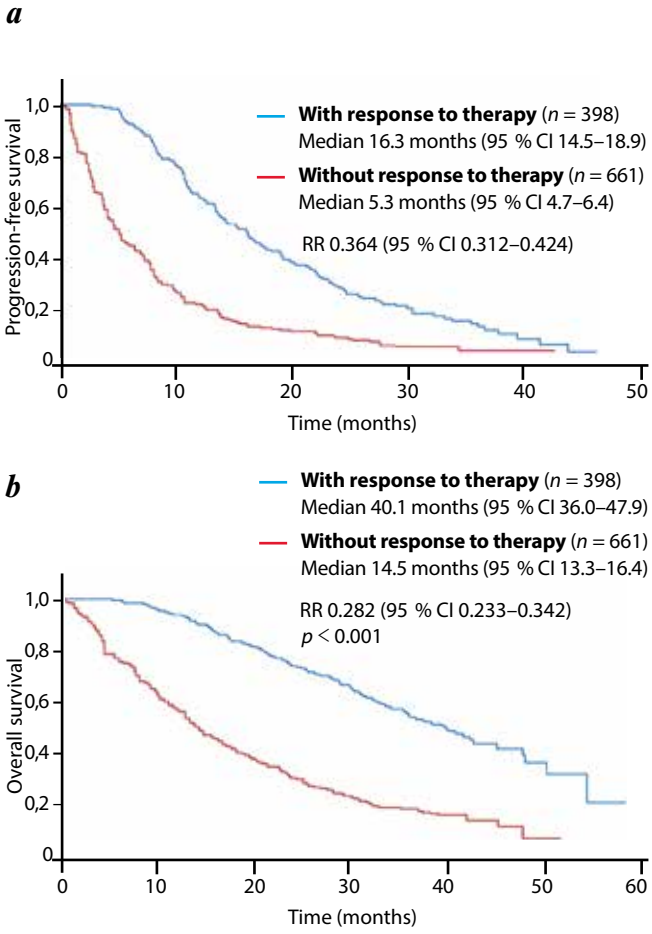
Axitinib is one of the first targeted drugs that showed effectiveness in the 2nd line therapy in direct comparison with sorafenib in the AXIS randomized phase III study

of patients with mRCC and progression in the course of the 1st line therapy. Axitinib significantly increased median PFS in the general patient population (6.7 months) and in patients who earlier received cytokine therapy (12.1 months) and sunitinib therapy (4.8 months) in comparison with sorafenib ($p < 0.0001$). Rate of objective response for axitinib was almost two times higher than for sorafenib (19 % vs. 9 %, $p = 0.0001$) [25].

In the AXIS study, the most common grade III and higher side effects were arterial hypertension, diarrhea, and fatigue in patients receiving axitinib, and palmar-plantar erythrodysesthesia, arterial hypertension, and diarrhea in the sorafenib group. Due to high rate of arterial hypertension associated with axitinib administration, the authors performed a detailed analysis and discovered that median OS in patients with diastolic arterial pressure (AP) of 90 mmHg and higher in the first 8 or 12 weeks of axitinib treatment was longer than in patients with AP lower than 90 mmHg. The same relationship held true for patients with systolic AP of 140 mmHg or higher and patients with systolic AP lower than 140 mmHg (Table 1). Multifactor analysis showed significant effect of diastolic AP of 90 mmHg and higher and systolic AP of 140 mmHg and higher on OS. RR for diastolic AP of 90 mmHg or higher was 0.627 (95 % CI 0.507–0.776; $p < 0.0001$) compared to diastolic AP lower than 90 mmHg. RR for systolic AP of 140 mmHg or higher compared to systolic AP lower than 140 mmHg was 0.490 (95 % CI 0.391–0.613; $p < 0.0001$). Evaluation of the effect of these factors on PFS in both treatment groups for 8- and 12-week therapy periods didn't show any significant differences [26].

B.I. Rini et al. have published an analysis of the results of treatment of patients with diagnosed arterial hypertension receiving axitinib and sorafenib in the AXIS study. After exclusion of patients with uncontrolled arterial hypertension, 145 (40.4 %) patients receiving axitinib and 103 (29.0 %) patients receiving sorafenib were singled out. The authors noted that grade III hypertension was observed in 55 (15.3 %) and 38 (10.7 %) patients, respectively; grade IV arterial hypertension was reported for 1 (0.3 %) patient in each group. An interruption of axitinib administration due to arterial hypertension was necessary for 46 (12.8 %) patients, dose reduction for 16 (4.5 %) patients, drug cancellation for 1 (0.3 %) patient. About 50 % of patients in the axitinib group received treatment for ≥ 9 months despite grade III or IV hypertension. Adverse events associated with arterial hypertension were diagnosed in < 1 % of patients receiving axitinib therapy. Arterial hypertension is more common for axitinib than for sorafenib. Arterial hypertension associated with axitinib administration rarely leads to treatment cancellation or cardiovascular complications. In authors» opinion, AP monitoring and corrective therapy allow to control arterial hypertension and to provide effective long-term antitumor treatment [27].

In 2014 a group of authors headed by B. Escudier published results of an analysis of patients of the AXIS study who received axitinib and previously received sunitinib or cytokines at the 1st line therapy. The researchers evaluated PFS and OS in the patient groups which were chosen according to presence or absence of objective response to the corresponding therapy, duration of previous therapy (< or ≥ median), and volume of tumor lesions (< or ≥ median initial total of the largest measured lesion diameters). The authors have shown that results of the previous treatment don't affect results of the 2nd line therapy with axitinib or sorafenib. PFS was longer in patients receiving axitinib and patients of the sorafenib group with small volume of tumor lesions who previously received sunitinib therapy. OS for the 2nd line targeted therapy was longer in patients who received previous therapy for a longer period of time, though these data weren't significant in the group of sequential sunitinib and axitinib therapy (Table 2). OS was also longer in patients with smaller volume of tumor lesions, but it was insignificant for the cytokines → axitinib sequence. Median OS in the axitinib group with previous sunitinib therapy was 33.7 (95 % CI 28.6–36.9) months and 33.6 (95 % CI 30.1–37.4) months



Progression-free survival (a) and overall survival (b) in patient groups with and without response to sunitinib therapy

in the sorafenib group ($p = 0.560$). Median OS in the axitinib group with previous cytokine therapy was 62.2 months (95 % CI 43.6–86.1) vs. 55.8 months (95 % CI 35.0–212.1) in the sorafenib group ($p = 0.139$). Median duration of previous treatment was 9.7 months in the sunitinib group and 6.5 months in the cytokine group. PFS was significantly higher for patients who received axitinib as the 2nd line therapy and previous long-term cytokine therapy in comparison with patients who received previous long-term sunitinib therapy (see Table 2). Duration of the 1st line therapy in patients receiving sorafenib as the 2nd line therapy didn»t affect PFS of these patients. In contrast, OS of patients receiving axitinib or sorafenib as the 2nd line therapy was significantly longer in patients with longer previous therapy, except patients receiving the sunitinib → axitinib sequence. The authors noted that in the AXIS study longer 1st line therapy allows to achieve better results in the 2nd line therapy, and absence of response to the 1st line therapy doesn't mean lack of positive clinical response to the 2nd line targeted therapy [28].

B.I. Rini et al. published results of a pharmacokinetic and pharmacodynamic study including 383 healthy volunteers, 181 patients with mRCC, and 26 patients with solid tumors in other locations from 17 different trials where they received axitinib. In the study, characteristics of axitinib administration were investigated using nonlinear mixed-effects modeling. Axitinib, similar to other VEGF inhibitors, has the following toxicity profile: fatigue, diarrhea, and arterial hypertension. Presence of arterial hypertension developed due to axitinib therapy was a favorable prognostic factor. Multivariate Cox regression analysis showed that increased AP is an independent prognostic factor associated with higher PFS and OS values, as well as higher rate of partial response in patients with mRCC. In conclusion, the authors noted that their results confirm advisability of axitinib dose titration for increasing diastolic AP and its use as a potential marker of effectiveness [24].

In 2015 the same authors published data of a randomized double-blind phase II study of effectiveness of axitinib titration in patients with mRCC. The authors evaluated pharmacokinetic parameters, AP level, and axitinib effectiveness. At the 1st stage of the 1st treatment course all patients received 5 mg of axitinib twice a day. Then in the absence of data on AP increase and AEs, patients were randomized 1:1, and in one of the groups axitinib/placebo dose was progressively increased to 7 mg twice a day (5 mg of axitinib + 2 mg of axitinib/placebo), and in the absence of induced arterial hypertension the dose was increased to 10 mg twice a day (5 mg of axitinib + 5 mg of axitinib/placebo). Patients lacking the necessary protocol conditions, unsuitable for randomization, continued the study without an increase in the axitinib dose. Subsequent pharmacokinetic studies and daily AP monitoring were performed. Data analysis showed that the area under curve for plasma concentration was higher in the patient group with full or partial response compared to patients with reported disease stabilization or disease progression, and was comparable to patients receiving placebo and non-randomized patients. There weren»t any significant correlations between AUC parameters in the general population and results of axitinib effectiveness. PFS of patients with ≥ 10 and ≥ 15 mmHg increase in AP was significantly

Table 1. *Effect of systolic and diastolic arterial pressure on overall survival and progression-free survival in the studied groups (AXIS) [26]*

Characteristics	Axitinib						Sorafenib					
	8 weeks			12 weeks			8 weeks			12 weeks		
	n	Median survival, months	Risk ratio; *p*	*n*	Median survival, months	Risk ratio; *p*	*n*	Median survival, months	Risk ratio; *p*	*n*	Median survival, months	Risk ratio; *p*
Overall survival												
Diastolic AP > 90 mmHg < 90 mmHg	 189 161	 21.3 13.9	0.775; $p = 0.034$	 203 132	 20.7 12.9	0.716; $p = 0.0ll$	 182 154	 21.1 15.8	0.724; $p = 0.012$	 187 141	 20.2 14.8	0.657; $p = 0.002$
Systolic AP > 140 mmHg < 140 mmHg	 217 133	 20.7 15.7	0.781; $p = 0.041$	 231 104	 20.7 17.0	0.753; $p = 0.032$	 225 111	 20.8 14.8	0.726; $p = 0.015$	 230 98	 19.9 14.8	0.715; $p = 0.015$
Progression-free survival												
Diastolic AP > 90 mmHg < 90 mmHg	 159 121	 8.1 8.3	1.009; $p = 0.523$	 160 80	 8.9 9.0	1.028; $p = 0.564$	 138 105	 4.8 4.7	0.922; $p = 0.284$	 124 74	 5.2 5.4	0.952; $p = 0.377$
Systolic AP > 140 mmHg < 140 mmHg	 179 101	 8.1 8.3	0.1148; $p = 0.830$	 168 72	 8.9 7.9	1.064; $p = 0.645$	 167 76	 4.8 4.8	0.897; $p = 0.232$	 145 53	 5.3 5.4	0.960; $p = 0.402$

Note. *AP – arterial pressure.*

Table 2. *Effectiveness of targeted therapy with axitinib and sorafenib depending on effectiveness of previous therapy (AXIS) [27]*

Characteristic	Previous sunitinib therapy		Предшествующая терапия цитокинами	
	< 9.7 months	≥ 9.7 months	< 6.5 months	≥ 6.5 months
Axitinib				
Number of patients, *n*	96	96	66	60
Median PFS, months (95 % CI)	6.4 (4.6–8.3)	6.6 (5.2–8.3)	8.6 (6.5–13.8)	15.7 (12.2–22.1)
RR (95 % CI)	0.998 (0.726–1.371)		1.966 (1.265–3.058)	
p	0.996		0.002	
Median OS, months (95 % CI)	11.7 (9.3–15.2)	18.1 (14.8–23.0)	26.3 (18.8–31.6)	MNR (28.0 – MNR)
RR (95 % CI)	1.242 (0.879–1.754)		1.983 (1.115–3.525)	
p	0.220		0.017	
Sorafenib				
Number of patients, *n*	95	99	59	66
Median PFS, months (95 % CI)	3.5 (1.9–4.7)	4.5 (3.0–6.5)	6.7 (5.6–9.5)	8.4 (7.2–10.2)
RR (95 % CI)	1.146 (0.824–1.593)		1.118 (0.747–1.675)	
p	0.431		0.580	
Median OS, months (95 % CI)	14.9 (10.5–18.0)	19.0 (15.0–23.9)	23.1 (17.3–31.9)	34.5 (27.8–34.5)
RR (95 % CI)	1.517 (1.073–2.416)		1.930 (1.133–3.289)	
p	0.018		0.014	

Note. *RR – risk ratio; CI – confidence interval; MNR – median not reached.*

higher. The researchers concluded that currently personalization of axitinib dosing regimen based on pharmacokinetic data and AP values shouldn»t be used as the only prognostic factor [29].

Therefore, in order to achieve maximum effectiveness of sequential targeted therapy, it is necessary to know the main principles of treatment optimization in patients with mRCC, including selection of 1st line drugs, optimal dosing and AE control, as well as therapy duration. Fast unsubstantiated change of drugs, as well as use of rotating regimens, didn»t show effectiveness in the studies. In case of manifested intolerance to sunitinib therapy, the 2/1 schedule with the full 50 mg/day dose can be used. Several studies have shown that objective response and arterial hypertension developed due to targeted therapy affect patients» survival. Depending on individual sensitivity, optimization of axitinib dose based on AP monitoring is possible in some patients.

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