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Evaluation of the Dynamics of Immune Response Checkpoints in Patients with Renal Cell Carcinoma Receiving Immunotherapy

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Abstract

Objective: To evaluate the effectiveness and tolerability of immunotherapy and to determine the immune response checkpoints in patients with renal cell carcinoma.

Materials and Methods: The study included 35 patients (average age 60, 77 years) with kidney cancer who received systemic therapy (including surgical treatment): 25 men and 10 women. All patients from the moment of inclusion in the study received immunotherapy - PD-1 inhibitor: nivolumab/pembrolizumab. No clinically significant side effects were noted during treatment, and the therapy was well tolerated. During immunotherapy, the following were evaluated: complete blood count, urinalysis, biochemical blood tests, coagulation profile, thyroid hormones, computed tomography of the chest and abdominal organs, and immune checkpoints (PD-1, PDL-1, B7-H3, sHLA, CD314-1, sULPB) were determined three times during the treatment period.

Results: The obtained data indicate that stabilization of the oncological process was registered in 18 patients (51.43%) and a partial response in 4 patients (11.43%). Disease progression was observed in 13 (37.14%) patients. No complete response to therapy was recorded. Lethal outcomes due to disease progression during therapy were recorded in 7 men (20% of cases) and 1 woman (2.86% of cases). Significantly more patients, both women and men, were alive at the end of the study. A pronounced trend of decreasing B7-H3 checkpoint indicators and increasing CD314-1, sHLA, PDL-1, and sULPB was noted.

Conclusion: The results, indicating disease control in 62.86% of cases in patients with renal cell carcinoma receiving immune checkpoint inhibitors as part of complex treatment, create a basis for further research to evaluate their potential in improving disease prognosis and life expectancy.

Keywords: Checkpoints; Renal cell carcinoma; Immunotherapy; PD-1; Nivolumab; Pembrolizumab

Introduction

Renal cell carcinoma (RCC) is the most common urological malignancy, imposing a significant burden on the healthcare system [1]. By the end of 2020, the proportion of patients with kidney cancer among all cancer patients in Russia was 4.8% [2]. The incidence of kidney cancer in 2020 was 21,362 patients, with a mortality rate of 8,455, and the lethality within a year of diagnosis was 14.1%. The average age of patients at diagnosis was 62 years. Approximately 25-30% of all patients had metastases at the time of diagnosis [3]. Renal cell carcinoma is the most common type of kidney cancer in adults (85%). Urothelial carcinoma accounts for 5-10% of kidney cancer cases. About 70% of kidney cancer cases are clear cell type, papillary type occurs in 10-15% of cases, and chromophobe type in 5% of cases [4]. Recognized risk factors for developing kidney cancer include smoking, obesity, and hypertension, while the role of alcohol and diabetes is still being studied [5]. Currently, the increase in incidence is attributed to improved early diagnostic measures. Kidney cancer has characteristics that make it a promising target for therapeutic approaches aimed at components of the immune system. Initial preclinical studies focused on the action of immune checkpoint inhibitors [6]. As a result, nivolumab and the combination of ipilimumab and nivolumab

were approved for the treatment of advanced renal cell carcinoma [7]. Subsequent studies led to the approval of a combined regimen of immune checkpoint inhibitors with vascular endothelial growth factor inhibitors [8]. Renal cell carcinoma responds poorly to conventional chemotherapy, and although treatments targeting the mechanistic target of rapamycin (mTOR) and vascular endothelial growth factor (VEGF) have increased therapeutic responses, almost all tumors eventually develop resistance to these molecularly targeted or anti-angiogenic treatments [9]. However, the question of choosing the optimal treatment regimen remains open [10]. The discovery of immune checkpoints has been a breakthrough in the treatment of kidney cancer. However, the anti-tumor immune response is not perfect and is suppressed by various tumor mechanisms that contribute to immune exhaustion and evasion of immune surveillance [11-14]. This study includes an evaluation of the effectiveness and safety of using immune checkpoint inhibitors in the treatment of patients with kidney cancer and an assessment of the liquid forms of key immune response checkpoints (PD-1, PDL-1, B7-H3, sHLA, CD314-1, sULPB). The advantages of determining soluble forms of immune checkpoints in the blood serum of patients include the ability to monitor them dynamically throughout the tumour process.

Objective

To evaluate the effectiveness and tolerability of immunotherapy and to determine the immune response checkpoints in patients with renal cell carcinoma.

Materials and Methods

The study included patients with kidney cancer who received anti-cancer drug therapy using immune checkpoint inhibitors at the Clinical Hospital 1 Medsi Otradnoye from 2021 to 2022. The study was approved by the local Ethics Committee (extract №4 dated 10.02.2021. “Approval of the Conduct of the Clinical Trial”). All patients signed informed consent to participate in the study. The primary objective of the study was to evaluate the frequency of objective responses to treatment and the frequency of control over the tumor process. Secondary objectives included evaluating overall survival, the safety profile of immuno-oncological drugs, and determining the liquid forms of immune response checkpoints in patients with renal cell carcinoma. The response to treatment was evaluated by the treating physician, and the effectiveness of anti-cancer drug therapy was assessed according to RECIST 1.1 criteria. An objective response was considered a complete or partial response, and control over the tumor process included complete, partial responses, and stabilization of the process. The severity of complications was assessed according to WHO recommendations and CTCAE criteria, v.5.0. Before the start of treatment and before each subsequent course of immunotherapy, blood was drawn to determine the liquid forms of key immune response checkpoints (PD-1, PDL-1, B7-H3, sHLA, CD314-1, sULPB). For structuring and processing statistical data, Microsoft Excel from the Microsoft Office software package and the STATISTICA statistical analysis software package were used. Results were evaluated as M ± m, and differences were considered significant at $p<0.05$. The study included 35 patients with mRCC: 25 (71.4%) men and 10 (28.6%) women, with histologically confirmed kidney cancer who received systemic anti-cancer drug therapy. The median observation time for patients was 5.2 months. The average age of patients was 60.77 years. The somatic status according to the ECOG classification was 0 for 5 (14.3%) patients, 1 for 28 (80%), and 2 for 2 (5.71%). Patient characteristics are presented in (Table 1).

Patients with the following histological variants of malignant kidney neoplasms were included in the study:

- Clear cell renal carcinoma in 29 (82.86%) patients
- Papillary renal carcinoma in 2 (5.71%) patients
- Chromophobe renal carcinoma in 1 (2.86%) patient
- Urothelial carcinoma in 1 (2.86%) patient

When assessing the prognosis of metastatic renal cell carcinoma (mRCC) using the IMDC scale, an unfavorable prognosis was registered in 12 (34.2%) patients, an intermediate prognosis in 20 (57.1%), and a favorable prognosis in 3 (8.6%). Surgical treatment had been previously performed on 26 (74.29%) patients, radiation therapy on 4 (11.43%), and anti-cancer drug therapy on 13 (37.14%). Two patients (5.71%) had four lines of previous therapy, seven patients (20%) had three lines, two patients (5.71%) had two lines, and 19 patients (54.29%) had one line of therapy. Five patients (14.29%) had no previous lines of therapy. All patients, from the moment of inclusion in the study, received anti-cancer drug therapy using immunotherapy with PD-1 inhibitors: nivolumab (480 mg every 4 weeks) or pembrolizumab (400 mg every 6 weeks or 200 mg every 2 weeks).

Results

The obtained data indicate that stabilization of the oncological process was registered in 18 patients (51.43%) and a partial response in 4 patients (11.43%). Disease progression was observed in 13 (37.14%) patients. No complete response to therapy was recorded. The characteristics of responses to therapy are presented in (Table 2). Lethal outcomes due to disease progression during therapy were recorded in 7 men (20% of cases) and 1 woman (2.86% of cases). Significantly more patients, both women and men, were alive at the end of the study. The obtained data also indicate that when using nivolumab (n=21), stabilization of the oncological process was registered in

8 patients (38.1%), a partial response in 3 patients (14.29%), and disease progression was observed in 10 patients (47.62%). When using pembrolizumab (n=14), stabilization of the oncological process was registered in 10 patients (71.43%), a partial response in 1 patient (7.14%), and disease progression was observed in 3 patients (21.43%). The characteristics of responses to therapy with different drugs are presented in (Table 3).

***Table 1**: Characteristics of RCC patients receiving immunotherapy (n = 35).*

Characteristic	Value (n=35)
Sex, n (%)	
male	25 (71,4)
female	10 (28,6)
Mean age, years	60,77
Stage, n (%)	
I	4 (11.43%)
II	5 (14.29%)
III	3 (8.57%)
IV	23 (65.71%)
ECOG status, n (%)	
0	5 (14,3%)
1	28 (80%)
≥2	2 (5.71%)
RCC type, n (%)	
1. clear cell	29 (82.86%)
2.papillary	2 (5.71%)
3. chromophobe	1 (2.86%)
4. urothelial	1 (2.86%)
Differentiation grade, n (%)	
G1	2 (5.71%)
G2	26 (74.29%)
G3	7 (20%)
Evaluation of Prognosis in Metastatic Renal Cell Carcinoma (mRCC) Using the IMDC Scale	
Unfavorable	12 (34,2%)
Intermediate	20 (57, 1%)
Favorable	3 (8,6%)
Previous Treatment, n (%)	
Surgical	26 (74.29%)
Radiotherapy	4 (11.43%)
Anticancer drug therapy	13 (37.14%)
Number of Lines of Previous Treatment (Number of Patients)	
0	5 (14.29%)
1	19 (54.29%)
2	2 (5.71%)
3	7 (20%)
4	2 (5.71%)

***Table 2**: Characteristics of treatment responses in patients.*

Treatment Response, n (%)	(n=35)
Complete response	0
Partial response	4 (11.43%)
Stabilization	18 (51.43%)
Progression	13 (37.14%)

***Table 3**: Characteristics of treatment responses in patients using different drugs.*

Response to treatment with different drugs, n (%)	(n=35)
Nivolumab	(n=21)
Partial response	3 (14.29%)
Stabilisation	8 (38.1%)
Progression	10 (47.62%)
Pembrolizumab	(n=14)
Partial response	1 (7.14%)
Stabilisation	10 (71.43%)
Progression	3 (21.43%)

The dynamics of immune checkpoints over three visits in patients receiving PD-1 inhibitors are presented in (Figures 1,2).

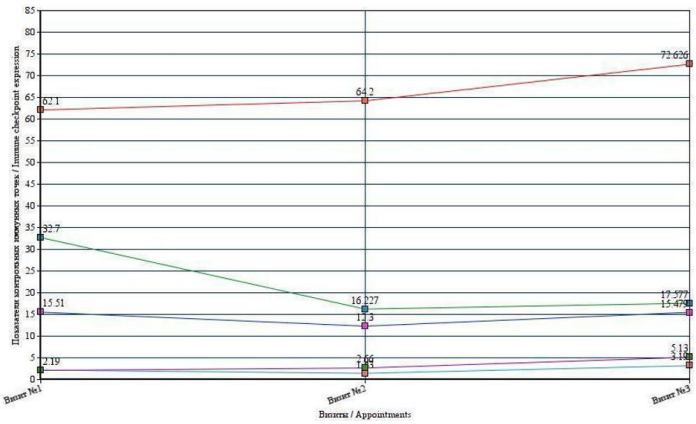

***Figure 1**: Dynamics of Immune Checkpoint Indicators (PD-1, PDL-1, B7-H3, CD314-1, sULPB) Over Three Visits in Patients Receiving PD-1 Inhibitors.*

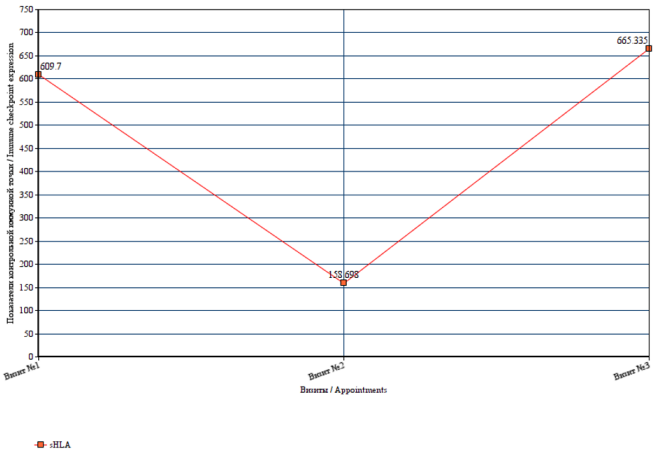

***Figure 2**: Dynamics of the sHLA Immune Checkpoint Indicator over Three Visits in All Patients Receiving PD-1 Inhibitors.*

The presented data indicate a pronounced trend of decreasing levels of the B7-H3 and sULPB checkpoints, and increasing levels of CD314-1, sHLA, and PDL-1. During the treatment, no clinically significant adverse events were noted, and the therapy was well tolerated. Adverse events were registered in 81.6% of patients, including 23.7% with grade III-IV severity. Most of the observed adverse events were grade I-II according to CTCAE 5.0 criteria and were corrected with symptomatic therapy. The most common adverse events were asthenia (26.3%), rash (15.8%), and loss of appetite (7.9%). In cases of mild adverse events, therapy was continued.

Conclusion

The obtained results indicate disease control in 62.86% of cases in patients with renal cell carcinoma, creating a basis for further research on the effectiveness of immune checkpoint inhibitor therapy as part of complex treatment to improve disease prognosis and life expectancy.

Author Contributions

- Data Collection and Processing: Semen akin IV, Mochalova AS, Kashanova AE.
- Data Analysis: Semenyakin IV, A.S. Mochalova AS,

KashanovaAE.

- Writing and Editing: Semenyakin IV, Mochalova AS, Kashanova AE.

Conflict of Interest

The authors declare no conflict of interest.

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