ASSOCIATION BETWEEN TIME FROM DIAGNOSIS TO INITIATION OF SYSTEMIC THERAPY OF METASTATIC RENAL CELL CARCINOMA WITH TREATMENT OUTCOME

POVEZANOST DUŽINE VREMENA OD DIJAGNOZE DO POČETKA SISTEMSKE TERAPIJE METASTAZNOG KARCINOMA BUBREŽNIH ĆELIJA SA ISHODOM LEČENJA

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Abstract

Introduction: In about 30% of cases, renal cell carcinoma (RCC) is detected initially in the metastatic stage (mRCC). The mainstay of mRCC treatment is anti-angiogenesis targeted therapy and immunotherapy which both have significantly prolonged progression-free survival and overall survival in patients with mRCC.

Aim: The aim of this study was to examine the association between the time interval from diagnosis of mRCC to the start of systemic therapy with the radiologically assessed best treatment response after 12 months of therapy.

Material and methods: This observational study included 85 patients diagnosed initially in the metastatic stage of RCC. All patients received single-agent systemic targeted therapy sunitinib. The minimum follow-up period was 12 months. The radiologic assessment was performed after every 3 months, and the RECIST criteria were used to evaluate the best treatment response.

Results: The mean time interval from mRCC diagnosis to the start of systemic targeted therapy was 3.5 ± 2.5 months, with a median of 2 months. No statistically significant association was observed between the best radiologically assessed treatment response after 12 months of therapy and the time interval from diagnosis of mRCC to the start of systemic targeted therapy (p = 0.7). Moreover, no statistically significant association was found between the best radiologically assessed treatment response after 12 months of therapy and a total number of metastatic sites at baseline.

Conclusion: No association was observed between the best radiologically assessed treatment response after 12 months of systemic targeted therapy, neither with the time interval from mRCC diagnosis to the start of systemic targeted therapy nor with the total number of metastatic sites in patients who were initially diagnosed with mRCC and received sunitinib in first-line setting.

Keywords: mRCC, systemic therapy, treatment response, observational study, sunitinib
Sažetak

Uvod: U oko 30% slučajeva karcinom bubrežnih ćelija (engl. Renal Cell Carcinoma - RCC) se otkriva u metastaznom stadiju (engl. metastatic RCC - mRCC). Okosnicu lečenja mRCC predstavljaju antiangiogeneza ciljana terapija i imunoterapija koje su pacijentima sa mRCC značajno produžile preživljavanje bez progresije i ukupno preživljavanje.

Cilj: Cilj ovog istraživanja je da se ispita povezanost između vremenskog intervala prosječna dužina vremena od trenutka postavljanja dijagnoze mRCC do početka sistemskih terapija sa radiografski procenjenim najboljim odgovorom posle 12 meseci terapije.


Rezultati: Prosečna dužina vremena od trenutka postavljanja dijagnoze mRCC do početka sistemskih ciljana terapije je iznosila 3,5 ± 2,5 meseca, sa medijanom od 2 meseca. Nije uočena statistički značajna povezanost između najboljeg radiografski procenjenog terapijskog odgovora posle 12 meseci terapije i vremenskog intervala od postavljanja dijagnoze mRCC do početka sistemskih ciljana terapije (p = 0.7). Takođe, nije uočena statistički značajna povezanost između ukupnog broja metastaznih mesta u momentu postavljanja dijagnoze mRCC i najboljeg radiografski procenjenog odgovora posle 12 meseci terapije.

Zaključak: Nije uočeno postojanje povezanosti između najboljeg radiografski procenjenog terapijskog odgovora posle 12 meseci primene sistemskih ciljana terapije ni sa vremenskim intervalom od postavljanja dijagnoze mRCC do početka sistemskih ciljana terapije, ni sa ukupnim brojem metastaznih mesta kod pacijenata sa dijagnozom inicijalno metastaznog RCC.

Introduction

Renal Cell Carcinoma (RCC) is the 6th leading cancer type in men and the 10th in women. The gender ratio is approximately 2:1 male-to-female. Histologically, the clear cell RCC is the most common type (1, 2).

In about 50% of newly diagnosed cases, the disease is found in the localized, non-metastatic stage (3, 4). At this stage, as being potentially curative, total and partial nephrectomy represent the mainstay of treatment (5, 6). After surgical treatment of a localized disease, local recurrence and/or metastases occur in 20 - 30% of patients, usually within a period of 3 years (7).

However, in about 30% of cases, RCC is primarily detected when the disease is already in the metastatic stage (mRCC) (1, 3). The importance of surgical treatment in this stage is less significant and includes cytoreductive nephrectomy (CN) and/or metastasectomy in certain indications (5, 6). It is resistant to treatment with conventional oncological modalities such as chemotherapy, radiotherapy, and hormone therapy (8).

The mainstay of mRCC treatment is VEGF-targeted antiangiogenic therapy and immunotherapy, which have both significantly prolonged progression-free survival and overall survival in patients with mRCC (5, 9). Currently, in Serbia, the only one available is first-line therapy, and patients may receive one of two drugs sunitinib (Sutent) or pazopanib (Votrient), both belonging to the same group of tyrosine kinase inhibitors (5, 10).

The proper time to start systemic targeted therapy is not yet precisely defined. According to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria, initiation of therapy in a period of less than one year from the diagnosis of mRCC is a poor prognostic factor (11). In several studies published to date, in patients with oligometastatic disease, delay in initiating therapy has not been associated with a poorer treatment outcome (6, 12, 13).

Therefore, the aim was to determine the radiologically assessed best treatment response after 12 months of therapy and its relationship with the time interval from diagnosis of mRCC to the start of systemic therapy. In addition, the goal was to examine an association between the total number of metastatic sites and the best radiologically assessed treatment response after 12 months of therapy.

Material and methods

Test sample

This observational retrospective study was performed at the Clinic of Urology, University Clinical Center of Serbia. The study group consisted of a total of 85 patients, of whom 68 (80%) were male and 17 (20%) female. All patients were older than 18 years. They all had a histopathologically confirmed diagnosis of clear cell RCC. The diagnosis was made after the CN or the kidney tumor biopsy in the initially metastatic stage of RCC. All patients started treatment in the period from January 1, 2012 to December 31, 2018. Follow-up lasted for a minimum of 12 months, ending on December 31, 2019 or until permanent
discontinuation of therapy for any reason before the end of the follow-up period.

Before initiating systemic targeted therapy, the presence of metastases was radiologically confirmed in all patients, based on the multi-detector row computed tomography (MDCT) of the chest, abdomen and pelvis. Prognostic risk assessment was performed using MSKCC score, and patients were stratified into groups with a good, intermediate and poor prognosis (14) (Table 1).

Table 1. Poor prognosis factors and prognostic groups according to MSKCC (Memorial Sloan-Kettering Cancer Center) prognostic score (14).

<table>
<thead>
<tr>
<th>Poor prognosis factors</th>
<th>Prognostic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Hemoglobin &lt; lower reference value</td>
<td>Good</td>
</tr>
<tr>
<td>2) LDH &gt; 1.5 x upper reference value</td>
<td>Intermediate</td>
</tr>
<tr>
<td>3) Corrected serum calcium &gt; 10 mg / dl (2.5mmol / L)</td>
<td>Poor</td>
</tr>
<tr>
<td>4) ECOG performance status ≥ 2</td>
<td></td>
</tr>
<tr>
<td>5) Time from diagnosis to the beginning of systemic therapy &lt; 1 year</td>
<td></td>
</tr>
</tbody>
</table>

LDH – lactate dehydrogenase; ECOG – Eastern Cooperative Oncology Group.

According to administrative rules proposed by the National Health Insurance Fund (NHIF), only patients with a good or intermediate prognosis can receive first-line treatment in Serbia (10).

Treatment protocol

All patients received sunitinib (Sutent) on a 2/1 dosing schedule (2-weeks-on and 1-week-off). The starting dose was 50 mg once daily and no reduction of dose was observed during the treatment. One cycle of therapy is completed after 6 weeks. After each cycle of therapy, performance status, complete blood count, biochemistry and side effects of therapy were assessed. After every two cycles of therapy, the radiologic assessment was performed following MDCT examination of the chest, abdomen and small pelvis. Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) were used to evaluate treatment response as stable disease, partial response, complete response or disease progression (16). The time from diagnosis of mRCC to the start of systemic therapy is defined as the time that has elapsed from the establishment of a histopathological diagnosis after CN or renal biopsy to the start of systemic targeted therapy. The best treatment response was defined as the sum of complete and partial responses registered after 12 months of therapy.

During the follow-up period of 12 months from the start of therapy, reasons for early treatment discontinuation were disease progression, death due to any reason, a significant side effect of therapy, or other reasons than that previously mentioned (loss of contact, personal request for discontinuation, etc.). Disease progression was defined as radiologic, clinical, or a combination of radiologic and clinical progression.

Statistical analysis

Continuous data are expressed as mean values with standard deviations or as medians with range where appropriate. Categorical data are presented by absolute numbers with percentages. Spearman rank correlation coefficient was used to test the association between ordinal and continuous variables. Statistical significance was tested at the level of 0.05, while the SPSS statistical software (SPSS for Windows, release 21.0, SPSSLS, Chicago, I) was used for statistical analysis.

Results

Out of a total number of 85 patients included in the study, 68 were male (80%) and 17 (20%) female. The mean age of the patients at the time of mRCC diagnosis was 59.2 ± 10.3 years.

According to MSKCC prognostic criteria, all patients had an intermediate prognosis. Time less than 12 months from diagnosis of mRCC to systemic treatment was found in 84 (98.83%) patients.

In a majority of patients, the ones initially diagnosed with metastatic disease have undergone CN prior to systemic therapy (80, 94.1%). According to the number of metastatic sites, 18 patients (21%) had one, 31 patients (37%) had two, and 36 patients (42%) had three or more sites with metastases. No statistically significant association was observed between the total number of metastases and the best radiologically assessed response to therapy after 12 months (p = 0.090). The demographic and clinical characteristics of patients with mRCC at the treatment baseline are presented in Table 2.

The mean time interval from mRCC diagnosis to the start of systemic targeted therapy was 3.5 ± 2.5 months, with a median of 2 months. In majority, treatment started 1 to 3 months after histopathologically confirmed diagnosis of mRCC (Figure 1).

After 12 months of treatment, 68 patients (80%) were evaluable for the best treatment response. Complete response was registered in one (2%), partial response in 9 (13%), and stable disease in 58 (85%) patients. Objective response was registered in 10 patients and the objective response rate was 15%. Treatment response was not evaluated in 17 patients (20%) since they discontinued therapy before the first evaluation. No statistically significant association was observed between the best radiologically assessed treatment response after 12 months
Table 2. Demographic and clinical characteristics of patients with mRCC before starting systemic therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>85 (100)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68 (80)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Age at the time of mRCC diagnosis</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>59.2 ± 10.3</td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>61 (35 – 81)</td>
</tr>
<tr>
<td>CN before starting therapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80 (94)</td>
</tr>
<tr>
<td>No</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Number of metastases at the beginning of therapy</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18 (21)</td>
</tr>
<tr>
<td>2</td>
<td>31 (37)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>36 (42)</td>
</tr>
</tbody>
</table>

Table 3. Evaluation of the best treatment response after 12 months of therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologically assessed best treatment response after 12 months of therapy</td>
<td>68/85 (80)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Objective response rate (CR + PR)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>58 (85)</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>17/85 (20)</td>
</tr>
</tbody>
</table>

Discussion

In patients diagnosed with mRCC, the proper time to start systemic targeted therapy is not well defined. According to MSKCC prognostic criteria, initiation of therapy in a period of less than one year from the diagnosis of mRCC is one of the factors of poor prognosis (11). In this study, the association between the time from diagnosis of mRCC to the start of systemic targeted therapy with radiologically assessed best treatment response after 12 months of therapy was examined. The mean time interval from the time of mRCC diagnosis to the start of systemic targeted therapy in the study was 3.5 ± 2.5, and the median was 2 months, which was not significantly different from the results reported so far in the literature (mean length 3.3, and median 1 month) (17). The results did not show a statistically significant correlation between radiologically assessed best treatment response and time interval from diagnosis of mRCC to initiation of targeted therapy (rs = -0.036; p = 0.744). Currently, there are still no validated diagnostic tests that can accurately predict the treatment response to systemic targeted therapy in patients with mRCC. This is important to note, given that according to the MSKCC prognostic score, one of the factors of poor prognosis is the initiation of systemic therapy in the first 12 months from the time of mRCC diagnosis (11). Therefore, the majority of patients initially diagnosed with mRCC will inevitably have an MSKCC median prognosis due to the existence of this risk factor in the overall score.

To the best of our knowledge, there are no published data with regard to the relationship between the time from diagnosis of mRCC to the start of systemic targeted therapy with radiologically assessed best treatment response after 12 months of therapy. Moreover, there are no published studies investigating only the population of patients initially diagnosed with mRCC. Therefore, a direct comparison of the results with data from the literature is not possible. However, according to the results of one retrospective study, it has been shown that patients who start...
therapy within the first 100 days from the time of diagnosis have a statistically significant faster progression of the disease (18). In this study, 27% of patients permanently discontinued therapy due to disease progression or death for any reason within 12 months of initiating targeted therapy.

The next segment of the study was to investigate the association between the total number of metastatic sites and the best radiologically assessed treatment response after 12 months of therapy in patients initially diagnosed with mRCC. The distribution of patients according to the number of metastatic sites was consistent with the results of other researchers (19). The analysis of data obtained in this study did not show a statistically significant correlation between the total number of metastatic sites and the best response to therapy after 12 months ($p = 0.090$). Based on the available published data, so far no study has examined the association between the total number of metastatic sites and the best response to therapy after 12 months. The number and location of metastases are not included as factors of poor prognosis in mRCC patients receiving systemic targeted therapy, in none of the validated prognostic scores, MSKCC and IMDC (International Metastatic RCC Database Consortium) (5, 6).

**Conclusion**

No association was observed between the best radiologically assessed treatment response after 12 months of therapy, either with the time interval from diagnosis of mRCC to the start of the systemic targeted therapy, or with the total number of metastatic sites. Delayed initiation of systemic targeted therapy in patients initially diagnosed with mRCC was not associated with poorer radiologically assessed best treatment response after 12 months of therapy.

**Literature**