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Clinical-Kidney cancer

The effect of a treatment delay on outcome in metastatic renal cell carcinoma

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Abstract

Objectives: To investigate if a first-line treatment delay (TD) can negatively affect the outcomes of patients affected by metastatic renal cancer.

Patients and methods: Patients with a diagnosis of metastatic renal cancer who were ineligible for active surveillance were included in the sample. A TD was defined as the time from the diagnosis of metastatic disease to the start of first-line therapy with tyrosine kinase inhibitors.

Results: A total of 835 patients were assessed and 635 were included in the final analysis. The median TD was 6.3 weeks. No significant differences were found in baseline characteristics between patients experiencing a TD below/equal to or above the median value, with the exceptions being the rate of bone metastases (25.3% vs. 35.9%) and advanced disease at diagnosis (34.7% vs. 54.9%). In patients who had received a previous nephrectomy for localized disease, the TD was 5.3 compared to 8.0 weeks for those with metastatic disease at diagnosis ($P = 0.001$). Among this latter group, 68.7% had received a cytoreductive nephrectomy. In patients with a TD below/equal to and above the median value, the median progression-free survival was 10.3 and 11.2 months, respectively (hazard ratio = 1.03; 95% confidence intervals, 0.86–1.22; $P = 0.78$); the median overall survival was 27.3 and 28.2 months, respectively (hazard ratio = 1.04; 95% confidence intervals, 0.86–1.27; $P = 0.68$). The lack of differences was confirmed when adjusted for prognostic factors and baseline characteristics.

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Conclusions: This study reports that patients with bone metastases and advanced disease at diagnosis have a significant probability of experiencing delayed first-line therapy of more than 6 weeks from the time of diagnosis. However, a TD does not significantly affect outcomes and survival.

Keywords: mRCC; First-line; Cytoreductive nephrectomy; Tyrosine kinase inhibitors; Treatment delay; Survival

1. Introduction

Renal cell carcinoma (RCC) is the sixth most common diagnosis of cancer in men and the eighth in women in the United States, with 63,990 new cases and 14,400 deaths estimated in 2017 [1]. In Europe, the incidence and mortality of RCC are estimated to be 71,739 and 31,293 cases per year, respectively [2,3].

In recent years, several agents targeting the vascular endothelia growth factor (VEGF), its receptor (VEGFR), the mammalian target of rapamycin (mTOR) axis, the antibody against the programmed death receptor-1 (PD1) and its ligand (PD-L1), and the cytotoxic T-lymphocyte antigen 4 have been approved for the treatment of metastatic RCC (mRCC) based on advantages in clinical outcomes demonstrated in large phase III clinical trials [4]. Recently, some studies have also reported that the prognostic class at the start of therapy may be predictive of a better outcome for cabozantinib or the combination of nivolumab plus ipilimumab compared to sunitinib [5,6]. Furthermore, analyses of a patient's baseline characteristics have revealed that a time period from nephrectomy to the start of medical therapy for metastatic disease of more than 1 year is a prognostic factor across most classifications (e.g., International MRCC Database Consortium—IMDC;—the Memorial Sloan Kettering Cancer Center—MSKCC); it maintains its prognostic role in both first and subsequent lines of therapy [7,8].

Despite patients with a recent diagnosis of metastatic disease generally asking for the immediate start of therapy, about 10% have low volume and/or slowly evolving disease and might be eligible for active surveillance. Furthermore, even those candidates for the immediate start of systemic therapy often have comorbidities that suggest the need to delay such treatment. Among this group, considerations are the time required to recover from surgical nephrectomy or manage other clinical conditions (e.g., pain, anemia, hypercalcemia); or delays related to the health system, such as hospital admission procedures to complete the staging of the disease or—especially in low-income countries—the time required to guarantee the reimbursement of funds for high-cost drugs. Recent evidence also suggests that the lack of a multidisciplinary team for the management of urological cancers may delay the start of treatment, with a negative impact on patient survival [9,10].

Considering the impressive results achieved in the last decade with the use of targeted agents in mRCC, leading to an increase in overall survival (OS), we aim to describe whether a treatment delay (TD) of first-line therapy after the diagnosis of metastatic disease can affect patient outcomes.

2. Patients and methods

2.1. Patients

In this analysis, we included consecutive patients with clear cell histology who received first-line therapy with tyrosine kinase inhibitors (TKIs) for mRCC at 16 cancer centers or tertiary hospitals in Italy. Patients were excluded if the TD was greater than 6 months, because they were probably candidates for active surveillance. Among the selected patients, only those with complete baseline characteristics such as histology and prognostic factors at the time of initiating first-line therapy were included in the final analysis.

The baseline characteristics required for inclusion were Eastern Cooperative Oncology Group (ECOG) performance status; extent of the disease; time from diagnosis to the start of therapy; and biochemical values for corrected calcium, hemoglobin, neutrophils, and platelet counts. The prognostic group at baseline was evaluated for each patient using the IMDC criteria [9]. Symptomatic patients were defined as those with an ECOG performance status ≥2.

The primary endpoint was to assess the correlation between the TD and progression-free survival (PFS) at the start of first-line of therapy with TKIs and OS. Subgroup analyses were performed to assess the impact of baseline characteristics such as the presence of metastatic disease at first diagnosis, the presence of symptoms and baseline IMDC prognostic factors.

2.2. Statistics

Baseline values were expressed as the median value. The baseline was defined as the start date of first-line treatment. The TD was evaluated from the diagnosis of metastatic disease to the start of first-line therapy. PFS was evaluated from the start of therapy to disease progression or death. Patients were assessed for progression every 12 weeks using the response evaluation criteria in solid tumors (v. 1.0) according to mandatory national guidelines required by the Agenzia Italiana del Farmaco. OS was evaluated from the start of first-line treatment, death, or the

last follow-up. All survivals were estimated using the Kaplan-Meier method and compared across groups using the log-rank test. A chi-square or *t* test was used to compare groups when appropriate. All the variables were considered to be significant if $P < 0.05$. The PASW software (Predictive Analytics SoftWare; v 21; IBM SPSS) was used for the analysis. The approval of the Ethics Committee was obtained for the study.

3. Results

3.1. Patients

Data regarding 835 patients treated in selected centers were analyzed. Of these patients, 155 had a TD of more than 6 months and were excluded from the analysis; 45 more were excluded because of the lack of complete data. This left a sample of 635 patients, and their baseline characteristics are reported in Table 1.

The median TD was 6.3 weeks (interquartile range: 3.4–11.1; Fig. 1). No significant differences in baseline characteristics were found between the patients with a TD below or equal to the median value and those with a TD above the median value; exceptions were the presence of bone metastases (25.3% vs. 35.9%) and metastases at the first occurrence of disease (34.7% vs. 54.9%; Table 1). The median TDs were 7.6 and 5.9 weeks in the patients with or without bone metastases ($P = 0.18$), respectively. In those who had received a previous nephrectomy for localized disease, the TD was 5.3 weeks and 8.0 weeks in those with metastatic disease at diagnosis ($P = 0.001$). Within this latter group, 68.7% of patients had received a cytoreductive nephrectomy.

3.2. Effect of TD on PFS

Among the 635 patients, the disease of 511 progressed during first-line treatment. The median PFS in the overall population was 11.1 months (95% confidence intervals [CI], 9.9–12.3). In patients with a TD ≤ the median value, the median PFS was 10.3 months compared to 11.2 months in patients with a TD > the median value; this difference was not significant (hazard ratio [HR] = 1.03; 95% confidence intervals [CI], 0.86–1.22; $P = 0.78$; Fig. 2).

When the difference was adjusted for baseline prognostic factors for PFS (Supplementary Table 1), no significant differences were found (HR = 0.96; 95% CI, 0.80–1.15; $P = 0.66$).

No significant differences in PFS were identified when cut-offs other than the median value were evaluated for the TD (Supplementary Table 2).

3.3. Effect of TD on OS

After a median follow-up of 47.6 months, 401 patients had died. The median OS in the overall population was 27.7 months (95% CI, 24.8–30.5). In patients with a TD ≤ the median value, the median OS was 27.3 months compared to 28.2 months in patients with a TD > the median value; this difference was not significant (HR = 1.04; 95% CI, 0.86–1.27; $P = 0.68$; Fig. 3).

Table 1
Baseline characteristics of the patients

Characteristics	Patients *n* = 635	TD ≤ 6.3 weeks *n* = 320	TD > 6.3 weeks *n* = 315	Chi-square *P value*
Median age (years)	63.2	62.1	63.9	0.11*
Male sex (%)	72.3	70.9	73.7	0.45
Nephrectomy (%)	85.4	84.4	86.3	0.48
Metastatic at diagnosis (%)	44.7	34.7	54.9	<0.001
ECOG PS ≥ 2 (%)	5.7	5.3	6.0	0.70
Sites of disease (%)				
Lung	65.8	63.8	67.9	0.27
Nodes	48.3	50.6	46.0	0.25
Bone	30.6	25.3	35.9	0.004
Liver	18.9	19.1	18.7	0.92
Adrenal gland	14.8	13.1	16.5	0.23
Brain	6.1	6.3	6.0	0.91
IMDC prognostic group at first-line (%)			0.075	
Good	24.9	28.8	21.0	
Intermediate	60.8	57.5	64.1	
Poor	14.4	13.8	14.9	
First-line therapy (%)				0.65
Sunitinib	76.4	75.6	77.1	
Pazopanib	23.6	24.4	22.9	

ECOG = Eastern Cooperative Oncology Group; IMDC = International MRCC Database Consortium; PS = performance status.
* = *t* test.

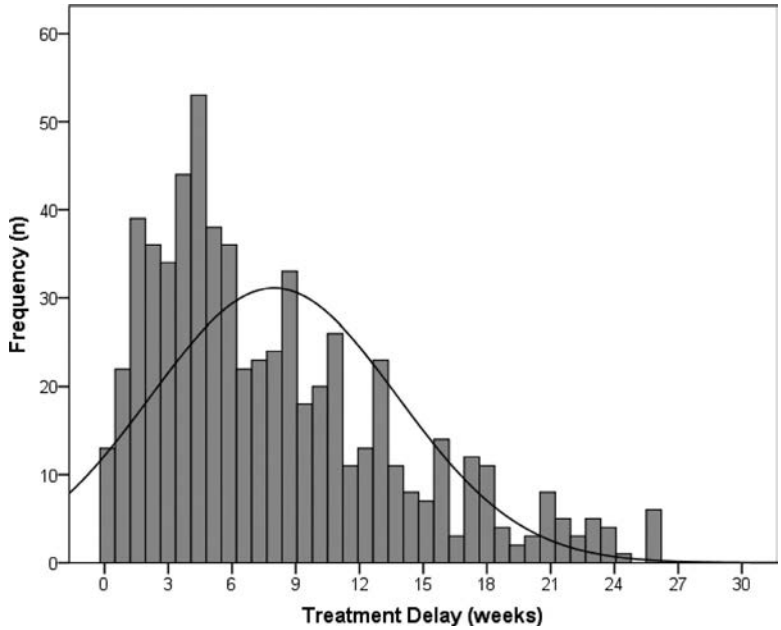

Figure 1. Frequency of treatment delay.

Even if the TD was adjusted for baseline prognostic factors (Supplementary Table 3), no significant differences were found (HR = 0.96; 95% CI, 0.77−1.17; $P = 0.59$).

Likewise, no significant differences in OS were identified when cut-offs other the median value were examined (Supplementary Table 2).

4. Discussion

To the best of our knowledge, this is the first study to investigate the prognostic role of a TD in patients affected by mRCC who are candidates to receive a VEGFR-TKI; several other studies have been conducted to evaluate the

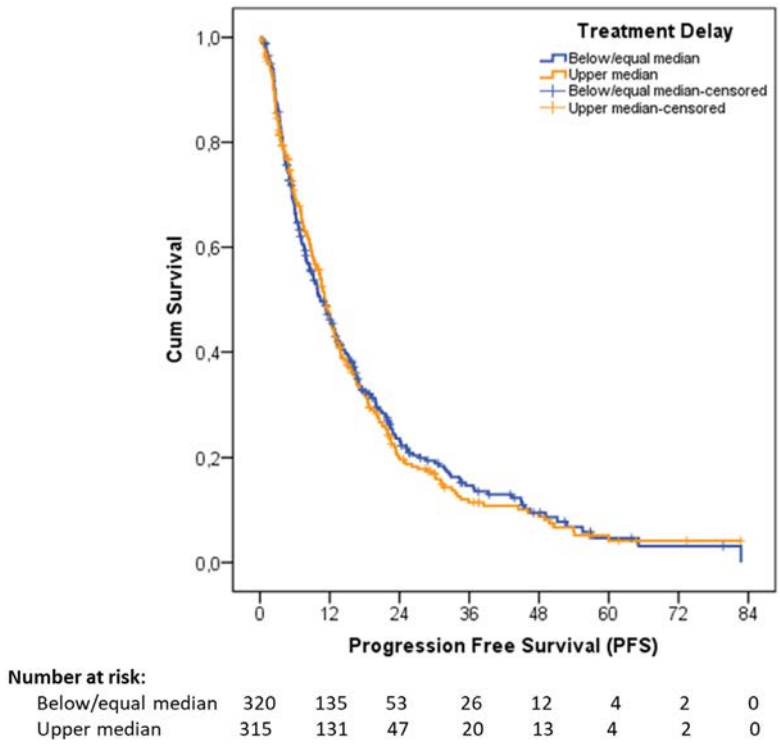

Figure 2. Kaplan-Meier curves for PFS according to treatment delay. PFS = progression-free survival.

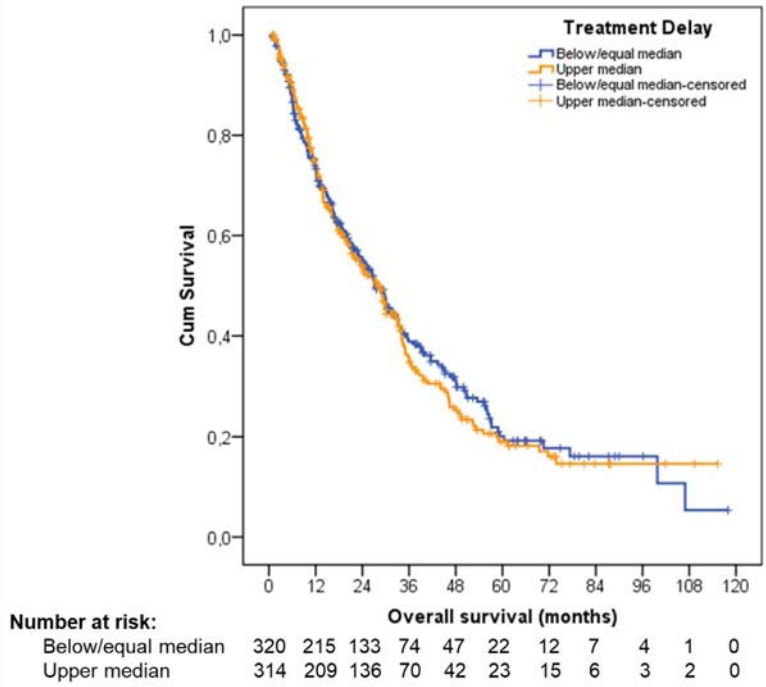

Figure 3. Kaplan-Meier curves for OS according to treatment delay. OS = overall survival.

impact of a TD on survival in different types of cancer, while others have tried to investigate the reasons for delays, with conflicting results.

The majority of studies in this area have investigated the impact of a TD on primary tumors. Becker et al. reported that delaying a nephrectomy for more than 3 months in non-metastatic kidney cancer patients was not related to worse outcomes when adjusted for other prognostic variables [11]. Other studies have reported that, in cases of the incidental diagnosis of a small renal mass of less than 4 cm, the length of time between diagnosis and surgical management has been reported to be over 2 years without any apparent impact on specific disease survival [12]. Moreover, in the prospective phase III trial that randomized mRCC patients to receive pazopanib or a placebo, there was no difference in OS, despite an obvious difference in PFS, and about 20% of patients in the placebo arm were progression free at 9 months [13]. In other tumors, a major analysis performed on more than 90,000 women who underwent a lumpectomy for breast cancer reported that each 60-day delay increased the breast cancer-specific mortality [14]. In lung cancer, a relationship between a TD and shorter survival was not identified in cases of localized or advanced disease, and the initial stage was the main predictor of survival [15,16].

Contrasting data are available for other urological neoplasia. In bladder cancer, it has been reported that a delay of more than 3 months between bladder resection and radical cystectomy was significantly associated with a pejorative-specific survival [17]. In addition, another large study of more than 2,500 patients reported a median time from transurethral bladder resection and radical cystectomy of 50 days. This study found a cut-off of 40 days for a worse survival outcome, suggesting this as a maximum time from diagnosis of muscle invasive bladder cancer to radical cystectomy [18]. These data are in contrast with a recent analysis where the TD adjusted for pathological local and lymph nodal stages was not found to be related to PFS or OS [19]. Several studies have analyzed the time between the initial diagnosis and surgery in testicular cancer. In this case, the median time is generally short, at about 7 days, and no data are available about the impact of delays on specific-cancer survival [12].

Our analysis was restricted to patients with metastatic disease eligible for VEGFR-TKI therapy, and we did not identify any differences in patients based on TDs; exceptions were bone involvement and the presence of metastases at diagnosis. Considering the prognostic role of the time from nephrectomy to the start of therapy, we performed a sensitivity analysis for patients with metastatic disease at the commencement of treatment and found no significant differences. Recently, a large randomized study investigated the noninferiority of sunitinib alone compared to sunitinib plus cytoreductive nephrectomy in mRCC patients with an intermediate or poor prognosis [20]. It reported that treatment with sunitinib alone is not inferior to the combined therapy and suggested that surgery can be avoided in the majority of patients. Our analysis found that a TD related to cytoreductive nephrectomy did not negatively affect the outcomes of first-line treatment and OS, meaning that this procedure can be safely proposed to eligible patients.

Likewise, no significant differences were found based on an ECOG performance status of 2.0, but patients with a

longer TD had a greater incidence of bone metastases and more frequently had metastatic disease at diagnosis. This difference may be explained by the need for: bone-targeted therapies (e.g., radiotherapy or surgery) in patients with bone metastases, as well as for those with metastatic disease at diagnosis; and histological diagnosis and cytoreductive nephrectomy before starting medical treatment.

In mRCC, a TD, also known as "active surveillance," is 1possible option for well-chosen patients. Recently, a prospective phase II trial of active surveillance conducted in 52 treatment-naive mRCC cases provided evidence that a period of close surveillance before further disease progression may be offered to newly diagnosed patients with mRCC who have a good performance status and a limited tumor burden, enabling treatment-related adverse events to be avoided and preserving quality of life [21]. Unfortunately, no specific criteria are available for selecting these patients, even if the change of prognostic class, as well as an increase in the tumor burden, has been suggested as a trigger for starting treatment, but without definitive evidence [22]. Recently, some authors performed a similar analysis of the effect of TDs in mRCC. They selected patients who had all been treated with a cytoreductive nephrectomy who delayed therapy for more than 6 months, with the longest delay being 20.1 months. Like our study, they found that a TD was not a predictor of mortality, even when adjusted for other prognostic variables [23].

Our study specifically selected patients who were ineligible for active surveillance, excluding those with a TD of more than 6 months. This population was judged to be eligible for a VEGFR-TKI and treatment had been delayed for several reasons that are not available in detail, with the exclusion of cytoreductive nephrectomy. The lack of information about the reasons for a TD is one of the major limitations of the present study. This is because a TD might have several causes, such as the time required for diagnostic procedures, a patient's initial refusal of therapy, the physician's preference or other reasons related to a hospital's organization.

This study has several other limitations, with the main one being its retrospective nature. Moreover, not all patient characteristics, such as the need for supportive therapy or radiotherapy, can be analyzed. The use of a cut-off value of 6.3 weeks is related to the characteristics of the studied population and may be different in other groups, even if a similar analysis was performed using different cut-offs without evidence of significant difference. Moreover, previous studies have revealed that a patient's culture, as well as the time before hospital admission, may play a role in TD, but these data were unavailable in our study.

This study did not find any differences in treatment outcomes and survival in patients who had a TD greater than 6 weeks. Similar results were confirmed for patients who received a cytoreductive nephrectomy compared to those who did not. Despite the apparent lack of a survival impact of a TD, this remains an important factor that should be evaluated in clinical practice. This is because early therapy may reduce certain tumor-related symptoms such as pain and the psychologically negative impact that it can have on patients.

Conflict of Interest

Authors did not report any conflicts of interest related to this work.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.03.005.

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