ORIGINAL RESEARCH

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Third-line Therapy for Metastatic Renal Cell Carcinoma and Its Effect on Quality of Life and Overall Survival: A National, Multicenter, Observational Study

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ABSTRACT Objective: The study aimed to evaluate the efficacy of targeted therapies used as the third-line treatment after first-line cytokine and second-line tyrosine kinase inhibitor (TKI) therapies in metastatic renal cell carcinoma (mRCC) patients and assess the quality of life (QoL) of patients. **Material and Methods:** This national, multicenter, non-interventional study included patients aged ≥18 years with histologically confirmed mRCC, receiving targeted therapies as the third-line treatment for the last one month. Overall survival (OS), progression-free survival (PFS), adverse events (AEs), and QoL were evaluated. **Results:** The study included 102 mRCC patients (74 males) (median age of 61 years). The median disease duration since diagnosis was 27.5 months (ranging 4-201 months). Of all the patients, 75.5% and 24.5% were receiving Axitinib and Everolimus, respectively, as third-line therapy. In all patients, the one-year PFS and OS rates were 62.9% and 79.9%, respectively. Seventy-one AEs (mostly mild) developed in 29 (28.4%) patients, fatigue being the most common (9.8%) AE. As compared to the baseline, no significant change was observed in the QoL scores of patients in the 12th month. The Axitinib and Everolimus groups did not differ significantly as regards to PFS and OS. Of the 11 patients with grade III-IV AEs, four were from the Everolimus group, and seven belonged to the Axitinib group. The QoL scores did not show a significant difference between the two groups except for that in the 12th month. **Conclusion:** Third-line therapy in mRCC patients was found to be effective and tolerable. Prolonged survival in mRCC patients receiving an increasing number of therapy lines requires further evaluation of QoL, considering it to be a part of treatment assessment.

Keywords: Clear-cell metastatic renal cell carcinoma; quality of life; survival

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Renal cell carcinoma (RCC) is a fatal urological malignancy. Among the most common cancers worldwide, RCC ranks 9th in males and 14th in females.[1] Though its incidence varies with geographical regions, RCC is more prevalent in developed countries.[2] RCC has shown a gradual increase in incidence in recent years.[1]

Treatment modalities for RCC have primarily undergone advancements and development in the last two decades.[2] Most RCC patients are either in the advanced or metastatic stage at diagnosis.[3] Besides the introduction of targeted therapies, significant changes have also been made in the treatment of metastatic RCC (mRCC). The advancements in treatment have prolonged the median survival rate and improved interest in this subject.[2,3]

Until recently, systemic therapy for the treatment of mRCC was limited to cytokines (interleukin-2 and interferon-alpha [IFN-α]). Cytokine therapy has been associated with low response rates and high toxicity.[4] Several molecular-targeted therapies have been introduced as the first-or second-line treatment.[4] Targeted therapies have been preferred over cytokines as they are associated with improved survival rates and show tolerable side effects.[5] Presently, the following groups of targeted therapies are employed in mRCC treatment: vascular endothelial growth factor (VEGF) antibodies, tyrosine kinase inhibitors (TKIs), and mammalian target of rapamycin (mTOR) inhibitors.[6]

An assessment of the quality of life (QoL) has been recently included as a trial outcome in oncology research. Although literature reports studies on the QoL of patients receiving first-or second-line treatment for mRCC, the number of studies on the assessment of QoL in mRCC patients receiving third-line treatment after first-line cytokine and second-line TKI therapies is limited. Therefore, the present study aimed to evaluate the efficacy of remedies targeted as the third-line treatment after first-line cytokine and second-line TKI therapies in mRCC patients and assess the QoL of these patients.

MATERIAL AND METHODS

PATIENTS

The study was designed as a national, multicenter, non-interventional study enrolling patients from 28 centers in 12 NUTS (Nomenclature of Territorial Units for Statistics) regions of Turkey. Patients aged ≥18 years with histologically confirmed mRCC who were undergoing targeted therapies as a third-line treatment since the last month were included in the study. The Clinical Research Ethics Committee of Kecioren Training and Research Hospital approved the study (approval No: B.10.4.ISM.4.06.68.49/; date: April 10, 2014). Informed consent was obtained from all the patients before they participated in the study. All the study procedures were conducted following the ethical standards of the institutional or national research committee and the later amendments of the 1964 Helsinki declaration or comparable ethical standards.

PROCEDURES

Data of patients, including demographic characteristics, medical histories, and characteristics of mRCC (histopathology, stage, metastasis, risk group, treatment status) of all the patients were recorded. The patients were followed-up for 12 months; clinical and laboratory data were collected at baseline, and at the 3rd, 6th, 9th, and 12th months as per the routine practice. Further, each patient was followed-up once to assess the overall survival (OS) before the site close-out visit. Progression-free survival (PFS) was defined as the time frame since enrollment to disease progression or death, whichever occurs first, and OS was defined as the time frame since enrollment to death or end of the study. Survival follow-up was conducted either via telephone or during the on-site visit if any. The assessment of adverse events (AEs) was based on the Common Terminology Criteria for Adverse Events (CTCAE V.4.03). The patients were also evaluated in two groups based on the medications that they were using as the third-line therapy: Axitinib group (n=77) and Everolimus group (n=25).

MEASUREMENTS

The following questionnaires were used for the assessment of QoL in the patients: 1) the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-15); 2) the FKSI-Disease-Related Symptoms (FKSI-DRS) subscale; and 3) the EuroQolFive-Dimensional Questionnaire, Three-Level version (EQ-

5D-3L). The FKSI-15 is a reliable and valid symptom index used for the evaluation of kidney cancer patients.[7] FKSI-DRS, 2007 version of the FKSI-15, is a reliable, valid, and responsive brief index probing the most significant symptoms related to advanced kidney cancer.[8] The EQ-5D-3L comprises the EQ-5D descriptive system and the EQ visual analog scale (EQ-VAS).[9] The EQ-5D descriptive system includes five dimensions- mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

STATISTICAL ANALYSIS

Data analyses were performed using the Predictive Analytics Software (PASW) Statistics for Windows version 18 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean, standard deviation, median, minimum, and maximum for quantitative variables and as numbers and percentages for categorical variables. The normality of data was tested using the visual (histogram and probability graphics) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Two-group and multiple-group comparisons for categorical variables were performed using the Chi-square test. The Fisher's exact test as performed in case the assumptions of the Chi-square test were unmet. Two-group comparisons of non-normally distributed numerical variables were performed using the Mann-Whitney U test. The Wilcoxon signed-rank test was used to evaluate QoL scores at 12 months with that of baseline scores. The Kaplan-Meier survival estimates were calculated for the analyses of OS and progression-free survival (PFS). Statistical significance was inferred at a type-I error level of 5%.

RESULTS

The study included 102 mRCC patients with a median age of 61 years (age range 24-83 years), of which 74 (72.5%) were males. The median disease duration was 27.5 months (ranging from 4-201 months) since diagnosis. The general characteristics of all the patients have been demonstrated in Table 1.

TABLE 1: General characteristics of the metastatic renal cell carcinoma patients.

Characteristics	
Age, years	60±12
Sex	
Male	74 (72.5)
Female	28 (27.5)
BMI, kg/m^2	27.6±5.24
Comorbidities	
Hypertension	17 (16.7)
Diabetes mellitus	12 (11.8)
Others	11 (10.8)
Histopathological type	
Clear Cell	84 (82.4)
Papillary	6 (5.9)
Chromophobe	6 (5.9)
Other	6 (5.9)
Site of Metastasis	
Lung	60 (58.8)
Bones	46 (45.1)
Liver	23 (22.5)
Lymph node	23 (22.5)
Brain	11 (10.8)
Number of metastatic sites	
1	55 (53.9)
2	33 (32.4)
≥3	14 (13.7)
ECOG performance status	
0	22 (21.6)
1	46 (45.1)
≥2	34 (33.3)
Stage at initial diagnosis	
I	9 (8.8)
II	24 (23.5)
III	15 (14.7)
IV	54 (52.9)
MSKCC score*	
Favorable	15 (14.9)
Intermediate	77 (76.2)
Poor	9 (8.9)

Data are presented as mean±standard deviation or number (%), where appropriate.
BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloan-Kettering Cancer Center.
*MSKCC risk was not available for 1 patient.

Of all patients, 84.3% underwent nephrectomy, and 5.9% had metastasectomy. All patients received IFN as first-line therapy. The median duration of treatment with IFN was 19.5 days (ranging from 1-1642 days). The primary reasons for discontinuation of IFN therapy included disease progression (50%) and intolerance (40.2%).

As the second-line treatment, patients received TKIs for a median duration of 302 days (ranging from 2-1,611 days), with the most frequently used TKIs being Sunitinib (53.9%) and Pazopanib (39.2%). The second-line TKI therapy was mainly discontinued due to disease progression (94.1%). Data on the second-line treatment with TKIs have been summarized in Table 2.

The patients were receiving Axitinib (75.5%) and Everolimus (24.5%) as the third-line therapy drugs at the time of enrollment into the study. The treatment records of patients during the 12-month follow-up period are summarized in Table 3.

During the follow-up period, 48.8% (n=49) presented the progression of the disease, while 34.3% (n=35) died. The Kaplan Meier analysis revealed that the 1-year PFS rate was 62.9% with a median PFS of 13+ months, and the 1-year OS rate was 79.9% with a median OS of 31+ months in all patients.

TABLE 2: Data on the patients' second-line treatment.

TKIs used	n (%)
Sunitinib	55 (53.9)
Pazopanib	40 (39.2)
Sorafenib	6 (5.9)
Sunitinib+Pazopanib	1 (1.0)
Best response to TKIs	
Partial Response	33 (32.4)
Stable Disease	38 (37.3)
Progressive Disease	31 (30.4)
Reasons for discontinuation of TKIs	
Progression	96 (94.1)
Intolerance	4 (3.9)
Adverse events	2 (2.0)

TKIs: Tyrosine kinase inhibitors.

A total of 71 AEs were detected in 29 (28.4%) patients. The most common AEs included fatigue (9.8%), diarrhea (8.8%), oral mucositis (5.9%), hy-

TABLE 3: Data on the patients' third-line treatment during the 12-month follow-up period.

	Months				
	0	3	6	9	12
Agents used	n (%)	n (%)	n (%)	n (%)	n (%)
Axitinib	77 (75.5)	62 (75.6)	31 (54.4)	19 (50)	13 (43.3)
Everolimus	25 (24.5)	15 (18.3)	21 (36.8)	11 (28.9)	7 (23.3)
Nivolumab		5 (6.1)	4 (7.1)	4 (10.5)	5 (16.7)
Palliative treatment			1 (1.8)	3 (8.0)	1 (3.3)
Gemcitabine, Oxaliplatin					1 (3.3)
Megestrol acetate					1 (3.3)
None				1 (2.6)	2 (6.7)
Total	102 (100.0)	82 (100.0)	57 (100.0)	38 (100.0)	30 (100.0)
Dose Modification		n (%)	n (%)	n (%)	n (%)
Escalation		7 (8.5)	5 (8.8)		
Discontinuation due to toxicity		13 (15.9)	6 (10.5)	5 (13.2)	4 (13.8)
Discontinuation due to disease progression			1 (1.8)		
Dose reduction		4 (4.9)	2 (3.5)		
None		58 (70.7)	43 (75.4)	33 (86.8)	25 (86.2)
Total		82 (100.0)	57 (100.0)	38 (100.0)	29 (100.0)
Response		n (%)	n (%)	n (%)	n (%)
Partial Response		15 (18.3)	9 (15.8)	4 (10.8)	2 (6.7)
Stable Disease		37 (45.1)	23 (40.3)	20 (54.1)	12 (40)
Progressive Disease		28 (34.1)	25 (43.9)	12 (32.4)	12 (40)
Not assessed		2(2.4)		1 (2.7)	4 (13.3)
Total		82 (100.0)	57 (100.0)	37 (100.0)	30 (100.0)

pertension (4.9%), cough (3.9%), and skin lesions (3.9%). Grade III-IV AEs (13 events) were determined in 11 patients.

In comparison to the median FKSI-DRS, FKSI-15, and EQ-5D-3L scores of the patients (14.0 [0-36], 25 [15-46], and 0.48 [-0.74-1], respectively) at baseline, no significant changes were observed in the corresponding scores at the 12th month (14.5 [1-36], 25 [13-45], and 0.51 [-0.74-1]; p=0.190, p=0.897, and p=0.673, respectively).

The characteristics of patients in Axitinib and Everolimus groups were similar except for the number of metastatic sites and the duration of the first-line treatment (Table 4).

The Kaplan-Meier analysis revealed that the median PFS was 12+ months in the Axitinib group and 9+ months in the Everolimus group with no significant difference between the treatment arms (p=0.243). The median OS was evaluated to be 28+ months in the Axitinib group and 18 months (ranging from 4.5-31.5 months) in the Everolimus group with no significant difference between the treatment arms (p=0.275).

The frequency of AEs was 28.6% in the Axitinib group and 28.0% in the Everolimus group. Of 11 pa-

TABLE 4: Characteristics of the patients receiving axitinib or everolimus as the third-line therapy.

	N	Axitinib Group	N	Everolimus Group	p
Age, years	77	62 (24-80)	25	58 (35-83)	0.703*
Sex	77				
Male		22 (28.6)	25	6 (24.0)	0.656**
Female		55 (71.4)		19 (76.0)	
BMI, kg/m^2	31	26.54 (19.92-44.53)	12	27.18 (19.47-39.45)	0.607*
Hypertension	77	13 (16.9)	25	4 (16.0)	1.000***
Diabetes Mellitus	77	9 (11.7)	25	3 (12.0)	1.000***
Histopathological Type	76		25		
Clear Cell		63 (82.9)		21 (84.0)	1.000***
Others		13 (17.1)		4 (16.0)	
Number of metastatic sites	77		25		
1		44 (57.1)		11 (44.0)	**0.009****
2		27 (35.1)		6 (24.0)	
≥3		6 (7.8)		8 (32.0)	
ECOG performance status	77		25		
0		15 (19.5)		7 (28.0)	0.253**
1		33 (42.9)		13 (52.0)	
≥2		29 (37.7)		5 (20.0)	
Stage at initial diagnosis	77		25		
I-II		25 (32.5)		8 (32.0)	0.965**
III-IV		52 (67.5)		17 (68.0)	
MSKCC score	76		25		
Favorable		10 (13.2)		5 (20.0)	0.448***
Intermediate		58 (76.3)		19 (76.0)	
Poor		8 (10.5)		1 (4.0)	
Duration of the first-line therapy, days	77	14 (1-1103)	25	44 (1-1642)	**0.019***
Duration of the second-line therapy, days	77	339 (25-1494)	25	214 (22-1611)	0.083*

*Mann-Whitney U test; **Chi-square test; *** Fisher's exact test

Data are presented as median (minimum-maximum) or number (%), where appropriate.

BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloan-Kettering Cancer Center.

tients with grade III-IV AEs, four belonged to the Everolimus group while seven were in the Axitinib group.

The QoL scores did not differ between the Axitinib and Everolimus groups, except for the FKSI-DRS score in the 12th month (Table 5). Moreover, when changes in the QoL scores of patients in the treatment arms were evaluated from the baseline to 12th month, a significant change was observed only in the FKSI-DRS score in the Everolimus group (Table 6).

DISCUSSION

Clinical studies have established favorable effects of targeted therapies on OS and PFS. It has been demonstrated that as compared to Sorafenib, Axitinib prolongs PFS in advanced RCC patients who fail to respond to prior systemic therapy and in advanced RCC patients showing disease progression after first-line therapy (containing sunitinib, bevacizumab plus IFN-α, temsirolimus, or cytokines).[10,11] Everolimus has also been demonstrated to prolong PFS when

TABLE 5: Comparison of the quality of life scores of the patients between the treatment arms.

	Axitinib		Everolimus		
	N	Median (Min-Max)	N	Median (Min-Max)	p*
FKSI-DRS					
Month 0	77	14 (0-27)	23	15 (1-36)	0.462
Month 12	20	14 (1-27)	10	16 (2-36)	**0.042**
FKSI-15					
Month 0	76	25 (15-38)	23	25 (15-46)	0.633
Month 12	20	24 (13-45)	10	25 (13-44)	0.465
EQ-5D-3L					
Month 0	76	0.494 (0.141-1)	24	0.480 (-0.74-1)	0.164
Month 12	20	0.507 (0.043-1)	10	0.480 (-0.74-1)	0.718

*Mann-Whitney U test.

Min-Max: Minimum-maximum; FKSI: Functional Assessment of Cancer Therapy-Kidney Symptom Index; FKSI-DRS: FKSI-Disease-Related Symptoms; EQ-5D-3L: EuroQol Five-Dimensional Questionnaire Three-Level version.

TABLE 6: Changes in the quality of life scores of the patients in the two treatment arms from baseline to 12th month.

	Month 0		Month 12		
	N	Median (Min-Max)	N	Median (Min-Max)	p*
FKSI-DRS					
Axitinib	20	13 (0-23)	20	14 (1-27)	0.977
Everolimus	10	12.5 (1-28)	10	16 (2-36)	**0.019**
FKSI-15					
Axitinib	20	25 (16-36)	20	24 (13-45)	0.733
Everolimus	10	25 (15-39)	10	25 (13-44)	0.438
EQ-5D-3L					
Axitinib	20	0.570 (0.141-1)	20	0.507 (0.043-1)	0.875
Everolimus	10	0.572 (0.043-1)	10	0.480 (-0.74-1)	0.612

*Wilcoxon signed-rank test.

Min-Max: Minimum-maximum; FKSI: Functional Assessment of Cancer Therapy-Kidney Symptom Index; FKSI-DRS: FKSI-Disease-Related Symptoms; EQ-5D-3L: EuroQol Five-Dimensional Questionnaire Three-Level version.

compared to placebo in advanced RCC patients who have received TKIs previously.[12] A study revealed no significant difference between the Everolimus (n=81) and Axitinib (n=45) groups (Everolimus and Axitinib used as second-line therapies) in terms of PFS and OS after the failure of first-line VEGF-targeted therapy.[13] A retrospective chart review (RCR) study conducted in the US found no significant difference in terms of OS or PFS at 12 months between two groups receiving Axitinib (OS and PFS rates were reported to be 83% and 56%, respectively) and Everolimus (OS and PFS rates were reported as 80% and 60%, respectively)as the second-line therapy.[14] Similarly, no significant differences were determined in terms of median PFS (12+ months and 9+ months, respectively; p=0.243) and median OS (28+ months and 18 months [range, 4.5-31.5 months]; p=0.275) in Axitinib and Everolimus groups in the present study. This hints that Axitinib may clinically favor longer PFS and OS.

Depending on the first-line therapy administered and the risk factors, nearly 33-79% of mRCC patients were well-suited to receive second-line therapy. The Memorial Sloan-Kettering Cancer Center (MSKCC) score has been stated to be a prognostic factor for survival in mRCC patients receiving targeted therapies.[15] The MSKCC risk groups and the first-line therapies have also been suggested as likely predictive factors for patients who would require second-line treatment in RCC.[16] Another chart review study from Japan documented that a shorter duration of first-line TKI treatment was associated with poorer prognosis.[17] A large international study investigating the use of third-line therapy in mRCC noted that patients having favorable or intermediate prognostic criteria had longer PFS and OS as compared to those with reduced risk.[18] In the present study, the duration of the first-line therapy was shorter in the Axitinib group than in the Everolimus group; however, no significant differences were found between the two groups in terms of the OS and PFS, duration of second-line therapy, and the distribution of patients as per the MSKCC risk scores.

As targeted therapies for mRCC treatment have resulted in significant improvement in PFS and OS, assessment of HRQoL is imperative for a therapeutic approach. While traditional cytokine-based therapies have unfavorable effects on HRQoL due to high levels of toxicity, targeted therapies are expected to have more positive impacts on HRQoL as they are more effective and tolerable.[19] Moreover, knowing the QoL outcomes of prior therapies in mRCC patients could guide the next therapeutic choices in the case of availability of the second-line and third-line therapeutic options.[20] A study conducted on mRCC patients with long-term survival (median 61 months; range- 36-133 months) in the US proved that the QoL score assessed by the FKSI-15 was comparable to the mean baseline score assessed in a phase III trial in a majority of patients who received VEGF-directed agents as the first-line therapy and mTOR inhibitor as the second-line therapy.[21] In the present study, the effects of third-line therapy on QoL were evaluated in mRCC patients who received second-line TKIs after first-line cytokine (IFN-α) therapy failed to respond. For all the three scales (FKSI-15, FKSI-DRS, and EQ-5D-3L), changes in scores at the 12th month for baseline were evaluated, and no significant difference was determined. The study also evaluated patients in two groups according to the third-line treatment that they were administered: Axitinib group and the Everolimus group. The QoL scores did not differ between the treatment groups, except for the FKSI-DRS score at the 12th month. Literature reports that Axitinib therapy either shows favorable effects or an acceptable negative effect on HRQoL and that HRQoL remains stable or improves throughout the Everolimus therapy.[21-24] Although Axitinib and Everolimus have different mechanisms of action and adverse event profiles, they were found to provide comparable QoL outcomes in the third-line treatment group in the present study. This may indicate that in the subsequent treatment line, the disease status affects QoL more than the drug. Accordingly, treatment decisions must be made considering the patients' status and specific side effects of drugs into account rather than assessing patients' QoL.

Adverse events are significant because of their impact on HRQoL. Contrary to the previous standard therapies, targeted therapies reportedly improve HRQoL; nevertheless, AEs (despite usually being mild and manageable) are likely to develop as the

treatment continues and may affect the patient's HRQoL.[25] Third-line therapy has been stated to have beneficial effects for mRCC patients who are resistant to previous therapies and an independent prognostic factor for longer OS. However, it has been emphasized that patients need to be monitored closely for the frequency of AEs.[26] Besides, the persistence of disease throughout the survival period, attributable to targeted therapies, and an increase in disease-related symptoms are also factors that unfavorably affect the QoL.[27] The most common AEs encountered during targeted therapies include fatigue; hypertension; diarrhea; hand-foot skin reaction; mucositis; proteinuria; dyspnea; neutropenia; thrombocytopenia; elevated levels of blood glucose, triglycerides, and cholesterol; and hypothyroidism.[28] In the present study, 28.4% of the patients developed AEs. The most commonly listed adverse events were fatigue (9.8%), diarrhea (8.8%), oral mucositis (5.9%), hypertension (4.9%), cough (3.9%), and skin lesions (3.9%). Of 11 patients with grade III-IV AEs, four belonged to the Everolimus group, and seven were from the Axitinib group.

In conclusion, third-line therapy (Axitinib and Everolimus) in mRCC patients following first-line cytokine and second-line TKI therapies was effective with a 1-year PFS of 62.9% and a 1-year OS of 79.9%. The therapy was tolerable with mostly mild AEs. No significant change was determined in the patients' QoL assessed at the 12th month for baseline. Individual evaluation of Axitinib and Everolimus groups did not reveal any significant difference between the groups in terms of PFS and OS. The QoL scores did not differ between the two treatment groups, except for the 12th-month FKSI-DRS score. Prolonged survival in the mRCC patients receiving an increasing number of therapy lines also necessitates an evaluation of patients' QoL, which must be considered as a part of the assessment of the treatment provided.

Declaration of Conflicting Interests

Hüseyin Öztürk and Birkan Aver are the employees of Pfizer Biopharmaceuticals Group, Istanbul, Turkey. The remaining Authors declare that that there is no conflict of interest.

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Conflict of Interest

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Authorship Contributions

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