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An evaluation of the clinical and treatment features of renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) is a significant cause of death, particularly in the elderly, and makes accounting for about 3% of all cancer cases. In kidney cancer, as in many other malignancies, treatment response and strategy are largely dependent on the prognosis at the time of diagnosis. Targeted therapies have been the subject of many studies in kidney cancer treatment in recent years. We looked into the objective response rate (ORR), overall survival (OS), progression-free survival (PFS), treatment options, adverse effects, and demographics of patients with kidney cancer in our study. Patients having a diagnosis of kidney cancer were included in the study, received tyrosine kinase inhibitor treatment, and were treated and followed up in our center between January 2005 and September 2017 at the Medical Oncology Clinic of Internal Medicine, Faculty of Medicine, Ondokuz Mayıs University. The files of these patients were analyzed retrospectively. 160 RCC patients in all who had treatment and followed up in our center were evaluated. The study included 62 patients who received tyrosine kinase inhibitors after first-line interferon in the metastatic period. The age range was 24-79 years old 24 to 79 years, with a median age of 62.7 years at the time of diagnosis. Forty-four (70.9%) patients were treated with sunitinib and 18 (29.1%) patients were treated with pazopanib in the first-line setting after metastatic interferon. PFS was 10.8 months for pazopanib and 11.4 months for sunitinib. OS was 23.6 months with for pazopanib and 25 months with for sunitinib therapy. ORR was 19% with sunitinib. Anemia was the most common hematologic adverse effect and fatigue was the most frequent non-hematologic side effect after sunitinib treatment, according to evaluations of side effects both hematological and non-hematological. according to evaluations of both hematological and non-hematological side effects. Individuals treated with sunitinib with pazopanib exhibited prolonged progression-free survival and overall survival. The results suggest that created treatments for m-RCC are successful.

Keywords: overall survival, kidney cell cancer, tyrosine kinase inhibitors

1. Introduction

Renal cancer makes about 3% of all cancer cases, of which 80% are clear cell carcinomas. It is one of the most common tumors and a leading cause of death for the elderly (1,2). The main risk factors for RCC are smoking, hypertension, obesity, diabetes mellitus (DM), analgesic drugs, genetic factors, cytotoxic chemotherapies, chronic HCV (3). It may spread lymphatically to the regional lymph nodes and hematogenously to the lungs, bones, adrenal glands, liver and contralateral kidney (4-6). Paraneoplastic (PNP) syndromes are detected in 40% of cases with RCC and occur with abnormal secretion of renal substances such as erythropoietin, renin, PTH, ACTH, glucagon, as well as various cytokines that are not secreted from the kidney (7,8). These factors are responsible for the appearance of symptoms such fever, anemia, and weight loss. Although RCC is mostly sporadic, 2-3% of cases are hereditary (8).

Histopathologically, renal cancer is classified under clear cell which is the most prevalent subtype, papillary, oncocytoma, chromophobe, eosinophilic, medullary, multilocular cystic and unclassifiable subtypes (9). Since the papillary RCC type is mostly detected in the first stage, approximately 75% of the patients have a good prognosis (10).

According to the International Metastatic Database Consortium (IMDC), there are good, moderate and poor pre-treatment risk factors. IMDC risk score is calculated based on the time from diagnosis to the start of systemic treatment, Karnofsky performance score, hemoglobin, calcium, neutrophil and platelet parameters. A score of 0 is considered as good risk, 1-2 as moderate risk and above 3 as poor risk. The five-year survival for metastatic disease ranges from 7.3% (1992-1995) to 11.7% (2007-2013) (11). Five-year survival rates were 15-30% in stage 4. Metastatic RCC are commonly chemotherapy resistant tumors. TKIs (sunitinib, pazopanib, cobazantinib, axitinib) prevent VEGF by blocking its intracellular conduction pathway and play an important role in the treatment of RCC (12). TKIs cause hematological (anemia) and non-hematological (fatigue, hypertension, hypothyroidism) side effects.

Various immunotherapy combination regimens, pembrolizumab and axitinib, nivolimumab and cabozantinib, pembrolizumab and lenvantinib, have been used in patients with higher disease burden and rapidly progressing RCC. In

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many studies comparing nivolimumab and ipilimumab, avelumab and axitinib treatments with single anti-angiogenic agents (sunitinib or pazopanib), it was observed that combination therapies gave better results in OS, PFS and complete response (CR) rates (13-17). In our study, demographic characteristics, side effects of the drugs, PFS, OS, ORR rates of RCC patients who received targeted therapies were investigated.

2. Matherials and Methods

The study included patients who were treated and followed up in our center for diagnosis of renal cell cancer between January 2005 and September 2017 and who received treatment with targeted therapy. The data of these patients were analyzed retrospectively. The study included 62 patients over the age of 18. Gender and age at diagnosis, complaints at presentation, pathological type of renal cancer and metastasis localization, complete blood count and biochemistry parameters at diagnosis, treatments given and side effects, response rate and survival data were evaluated from the patients' files. The interval between the date of diagnosis and the last follow-up or death occurs as OS. PFS is the amount of time from the start of treatment until the disease progresses or the treatment plan is adjusted. ORR is the sum of complete and partial response rates.

SPSS 21.0 software was used for analysis of all data. The symbol for standard deviation was expressed as (±). The independent variable t test was used to compare parametric variables between groups. The chi-square test was used to evaluate nonparametric variables. For survival analysis, the Kaplan-Meier test was employed. The confidence interval was assigned at 95%. A p value of <0.05 was deemed significant.

3. Results

The data of 160 RCC patients, 90 (56%) males and 70 (44%) females who were treated and followed up in our center were evaluated. Among those, 62 patients have received first-line TKI after interferon and were included in the study. Men accounted for 74% of all the patients and the OS was similar for both sexes (31.8 months for men and 30.3 months for women p=0.13). The PFS was 15 months for women and 21 months for men, the difference was not statistically significant (p=0.14). The median age of the patients at diagnosis was 62.7 years (IQR: 24-79). The ages of women and men were similar (63.3 and 62.5 years, respectively; p= 0.17). The number of patients with ECOG 0-1 was 50. The median OS was 40 months (see the Supplementary Appendix Fig. 1). Additionally, 12.5% of all patients survived for three years. When the complaints at presentation were compared, 16 patients (25.8%) presented with hematuria, 12 (19.4%) with fatigue, 10 (16.1%) with left flank pain, 5 (8.1%) with right flank pain, and the other patients presented with cough, abdominal mass, weight loss, lower extremity pain, nausea, and testicular swelling. The most common histopathologic subtype was clear cell type in 47 patients (75.4%), papillary type in 8 (12.9%) and chromophobe type in 2 (3.2%). OS of clear cell type was 32 months, papillary 27 months and chromophobe 27 months. Pathologic subtype and OS did not have a statistically significant relationship (p=0.15).

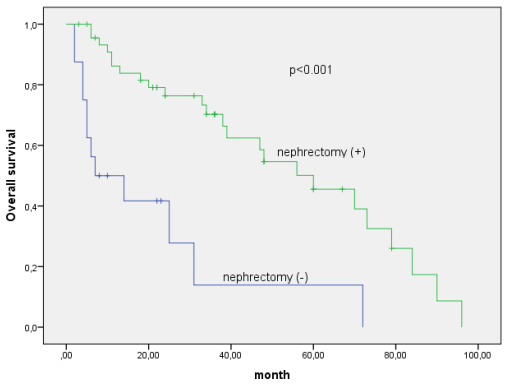

Fig. 1. Overall survival and nephrectomy

Table 1. Demographic characteristics

Age, years (IQR)	62.7(24-79)
Gender, n (%)	
Female	16 (25,8)
Male	46 (74,2)
ECOG, n (%)	
0	24 (38,7)
≥1	38 (51,3)
Presenting complaint, n (%)	
Hematuria	16 (25,8)
Fatigue	12 (19,4)
Side pain	10 (16,1)
Other	24 (38,7)
Nephrectomy, n (%)	
No	16 (25,8)
Yes	46 (74,2)
Histologic type, n (%)	
Clear cell	47 (75,4)
Papillary	8 (12,9)
Chromophobe	2 (3,2)
Side of metastasis, n(%)	
Diffuse lymph node	21 (34)
Lung	15 (24)
Other	26 (42)
Treatment, n (%) 1 lines after IFN	
Sunitinib	44 (70,9)
Pazopanib	18 (29,1)

Depending to the site of metastasis, 34% had metastasis to diffuse lymph nodes, 24% to lung, and 42% to other localizations. Nephrectomy was performed in 46 patients (74.2%). Demographic characteristics are summarized in Table 1. With a median OS of 60 months in the nephrectomy group and a median OS of 7 months in the non-nephrectomy group, the effect of nephrectomy on OS was statistically significant ($p<0.001$) (Fig. 1). In our study, all patients received interferon; targeted therapies were preferred for patients who could not tolerate IFN treatment or who progressed afterwards. In first-line treatment metastatic RCC after interferon, 44 (70.9%) patients received sunitinib and 18 (29.1%) pazopanib. There are no specific criteria when choosing sunitinib or pazopanib. The physician was chosen based on his/her preference. However, in general, pazopanib was preferred in older and frail patients. The PFS for sunitinib and pazopanib in our trial was 11.4 and 10.8 months, respectively. The OS was 25 months in sunitinib and 23.6 months in pazopanib. The response rate was 6% complete response, 13% partial response and 20% progression in sunitinib-treated patients. The response rate with pazopanib was 5% complete response, 7% partial response and 25% progression. When side effects were evaluated hematologically and non-hematologically, among the patients receiving sunitinib treatment, the most common hematologic side effect was anemia and the most common non-hematologic side effect was fatigue. The most common side effects were fatigue and nausea in the patient receiving pazopanib. With both sunitinib and pazopanib, side effects were seen at grade 1 level and it was not necessary to discontinue or interrupt the treatment.

4. Discussion

RCC is one of the most common diseases and a major cause of death, particularly in older individuals. Numerous clinical studies have been conducted on the disease. Especially the effects of targeted drugs on survival are important for clinical trials. The course of therapy for RCC is mostly based on the prognosis of the patient at the time of diagnosis, similar to many other cancers. Our research aimed to discover more about the clinical and demographic features, available treatments, side effects, and response rates of individuals with RCC.

In our study, the median age at diagnosis was 62.7 years, and the male to female ratio was 3:1. In the study by Lipworth et al. the average age at diagnosis was 64 years, 1.5 times higher in males than females. Similar rates were observed in other studies on renal cancer (18).

In our study, 25.8% of the patients presented to the hospital with hematuria which is the most common presentation. Patients with localized disease may present with a wide range of symptoms or laboratory abnormalities or may be diagnosed incidentally. In a review of 309 patients with RCC, the most common symptoms were weight loss, hematuria, abdominal mass, and pain (11). Similar findings were found in other studies.

In our study, clear cell type was the most common histopathologic type with 75.4%. Patard et al. reported clear cell 60-70%, papillary 5-15%, chromophobe and oncocytic 5-10%, collecting duct <1%, which is similar to our study (19). The OS was 32 months in patients with clear cells, 31 months in sarcomoid cells, and 27 months in chromophobe and papillary cells. There was no significant difference between the OS and the pathologic type. In previous studies, sarcomatoid type was found to has worse prognosis with median survival of 6.6 months (20). The low patient volume in our cohort could be the reason for difference of results. A greater number of patients could be used to conduct more thorough investigations.

A retrospective study conducted in 2015 involving a total of 351 metastatic RCC patients from 18 clinics showed that primary nephrectomy gave better results on OS. In this study, the group that underwent a primary nephrectomy had an OS of 38.1 months, while the group that did not have one had an OS of 16.4 months ($p<0.001$) (21). In our study, 46 patients had primary nephrectomy, but 16 patients could not be treated with nephrectomy. The median OS between the patient groups according to nephrectomy status was 60 months and 7 months ($p<0.001$), respectively, and primary nephrectomy was associated with longer OS.

Male and female metastasis rates were similar in our study; 34% spread to diffuse lymph nodes, 24% to the lung, and 42% to other localizations. According to previous studies, 75% of m-RCC metastasized to the lung, 36% to soft tissues, 20% to bones, 18% to the liver, 8% to the skin, and 8% to the central nervous system (22,23).

For sunitinib, the median PFS was 11.4 months (95% CI 1-48 months) and 10.8 months (95% CI 1-42 months) for pazopanib. OS was 25 months in sunitinib and 23.6 months in pazopanib. In similar studies in the literature, median PFS was 9.6 (95% CI 8.2-11.0 months) for sunitinib and 11.6 (95% CI 1-17 months) for pazopanib (24,25).

Table 2. Various clinical trials of sunitinib treatment

Clinical trials	Patient, n	Median OS (month)	Median PFS (month)	ORR (%)
OMU Oncology BD	44	25	11,4	19
İ.Ü.Institute of Oncology	105	21	9	20
Gore et al.	4371	18,4	10,9	17
Schnading et al.	134	15,5	7,5	16,4

The results are similar to our study. When we compared our response rates in patients receiving sunitinib treatment with the study of Gore et al., ORR was 19% and 17%, respectively; PFS was 11.4 and 10.9 months, respectively; and OS was 25 and 18.4 months, respectively. The results were consistent with other studies (26, 27). Comparison of the efficacy of sunitinib with other studies is summarized in Table 2.

Anemia was the most frequent hematologic side effect and fatigue was the most prevalent non-hematologic side effect among patients taking sunitinib therapy when side effects were evaluated both hematologically and non-hematologically. Patients who received pazopanib most frequently experienced nausea and fatigue as adverse effects. In a study conducted in Poland, side effects in 39 patients treated with sunitinib were: hypertension, neutropenia, thrombocytopenia, stomatitis and hand-foot syndrome (43.6%, 38.5%, 33.3%, 33.3% and 12.8%, respectively). Grade 3 serious side effects were found for fatigue and hypertension (28).

For metastatic RCC, TKI can be the preferred medication. Both PFS and OS have increased as a result of these treatments. Sunitinib is a tolerable medication for metastatic RCC because of its poor efficacy and low possibility for adverse effects. Our study's results were in line with previous research. The results imply that tailored treatments for m-RCC are successful. The OS was observed to be benefited by nephrectomy.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: N.M., G.D., Design: N.M., G.D., Data Collection or Processing: N.M., G.D., Analysis or Interpretation: N.M., G.D., Literature Search: N.M., G.D., Writing: N.M., G.D.

Ethical Statement

Ondokuz Mayıs University Ethics Committee/Approval Date-No: December 15, 2017- B.30.2.ODM.0.20.08/1258.

References

1. World Cancer Report-2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics 2007. Cancer. J Clin 2007; 57: 43-66.42
3. Luzzatto L, Pandolfi PP. Causality and chance in the development of cancer. N Engl J Med. 2015;373(16):1579
4. Estig D, Ahlering TE, Lieskovsky G, et ai:Experience with fossarecurrance of renal cell carcinoma. J Urol, 147: 1491, 1992
5. Gelister JSK, Falzon M, Crawford R, Chapple CR, et al:Urinary tractmetastasis from renal carcinoma. Br J Urol 1992;69: 250,
6. Williams R.D:Renal, perirenal and ureteral neoplasms. In Adult and Pediatric J. Urology. Edited by J. Y. Gillenwater, J. T. Grayhack, S. S. Howards, J. W. Ducked. Chicago-London Boca Raton. Yearbook Medical Publishers inc:Vol. 1, chapt 16, pp: 1988;513-554,
7. Gold PJ, Fefer A, Thompson JA:Paraneoplastic manifestations ofrenal cell carcinoma. Semin Urol Oncol 1996; 14:216-222.
8. Bellocco, R., Pasquali, E., Rota, M., Bagnardi, V., Tramacere, I., Scotti, L.,et al. Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. Annals of oncology, mds022. ;2002
9. McLaughlin JK, Linblad P, Mellemgaard A., et. al:International renal cell cancer study:I. Tobacco use. Int. J. Cancer 1995; 60:194-198.
10. Beck, S.D., Patel, M.I., Snyder, M.E., Kattan, M.W., Motzer, R.J., Reuter, V.E. ve diğerleri. Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma. Ann Surg Oncol, 2004;11 (1), 71-77.
11. Kidney Cancer, NCCN Guidelines Version 1.2013. (2013).
12. Atkins MB. Management of advanced renal cancer. Kidney Int 2005; 67:2069.
13. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol 2020; 21:1563.
14. Cella D, Motzer RJ, Suarez C, et al. Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial. Lancet Oncol 2022; 23:292.
15. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2019; 30:706.
16. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open 2020; 5:e001079.
17. Regan MM, Jegede OA, Mantia CM, et al. Treatment-free Survival after Immune Checkpoint Inhibitor Therapy versus Targeted Therapy for Advanced Renal Cell Carcinoma: 42-Month Results of the CheckMate 214 Trial. Clin Cancer Res 2021; 27:6687.
18. Lipworth, L.,Tarone, R. E., McLaughlin, J. K. Theepidemiology of renalcellcar-cinoma. TheJournal of urology, 2006, 176.6: 2353-2358.
19. Patard JJ, Leray E, Rioux-Leclercq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005, 23 (12), 2763-2771.
20. Karakiewicz, P.I., Hutterer, G.C., Trinh, Q.D., Pantuck, A.J., Klatte, T., Lam, J.S. ve diğerleri. Unclassified renal cell carcinoma: an analysis of 85 cases. BJU Int, 2007; 100 (4), 802-808.)
21. Mathieu R, Pignot G, Ingles A, Crepel M, Bigot P, Bernhard JC, Joly F, Guy L, Ravaud A, Azzouzi AR, Gravis G, Chevreau C, Zini L, Lang H, Pfister C, Lechevallier E, Fais PO, Berger J, Vayleux B, Roupret M, Audenet F, Descazeaud A, Rigaud J, Machiels JP, Staehler M, Salomon L, Ferriere JM, Kleinclauss F, Bensalah K, Patard JJ. Nephrectomy improves overall survival in patients with metastatic renal cell carcinoma in cases of favorable

MSKCC or ECOG prognostic features. Urol Oncol. 2015 Aug;33(8):339.e9-15. doi: 10.1016/j.urolonc.2015.05.014. Epub 2015 Jun 16. PMID: 26087971

22. Golimbu, M., Joshi, P., Sperber, A., Tessler, A., Al-Askari, S.,Morales, P. Renal cell carcinoma: survival and prognostic factors. Urology, 1986; 27 (4), 291-301.

23. Maldazys, J.D.,deKernion, J.B. Prognostic factors in metastatic renal carcinoma. J Urol, 1986; 136 (2), 376-379.

24. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356(2):115–24.

25. Schnadig ID, Hutson TE, Chung H, Dhanda R, Halm M, Forsyth M, et al. Dosing patterns, toxicity, and outcomesin patients treated with first-line sunitinib foradvanced renal cell carcinoma in community-based practices. Clin Genitourin Cancer 2014;12(6):413–21.

26. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009;10(8):757–63.

27. Schnadig ID, Hutson TE, Chung H, Dhanda R, Halm M, Forsyth M, et al. Dosing patterns, toxicity, and outcomes in patients treated with first-line sunitinib for advanced renal cell carcinoma in community-based practices. Clin Genitourin Cancer 2014;12(6):413–21

28. Domagala-Haduch M, Cedrych I, Jasiowka M, Niemiec M, Skotnicki P. Analysis of adverse events of sunitinib in patients treated for advanced renal cell carcinoma. Arch Med Sci. 2016;12(2).