Research Article

Rechallenge Immunotherapy in Former Interferon-Treated Patients with Metastatic Renal Cell Carcinoma

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Abstract

Objectives: The management of metastatic renal cell carcinoma (RCC) in the third-line setting presents significant challenges due to limited data on treatment options beyond first-line and second-line therapies. Immunotherapy rechallenge with immune checkpoint inhibitors has emerged as a potential strategy for selected patients who previously responded to initial treatment but experienced disease progression. This study aimed to evaluate the effectiveness of nivolumab in patients previously treated with interferon alpha and anti-vascular endothelial growth factor therapies.

Methods: A total of 54 adult patients with metastatic RCC were included. Demographic data, International Metastatic RCC Database Consortium (IMDC) risk scores, pre-treatment laboratory findings, and previous treatment lines were reviewed retrospectively. Overall and progression-free survival (OS and PFS) outcomes were analyzed by statistical tests.

Results: The median OS and PFS were 25.3 (95% CI: 22.3-28.3) and 9.7 (95% CI: 4.8-14.6) months, respectively. No significant relationships were found between OS and sex (p=0.585), age (< vs. ≥65 years, p=0.98), IMDC risk groups (p=0.39), second-line treatment (pazopanib vs. sunitinib, p=0.425) or nivolumab line (III vs. IV, p=0.249). PFS was consistent with OS in this sense.

Conclusion: The median PFS of 9.7 months surpassed previous data on immunotherapy rechallenge, suggesting a potential benefit of interferon alfa in enhancing immunotherapy response.

Keywords: Immunotherapy, metastatic renal cell carcinoma, interferon alpha, nivolumab.

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Renal cell carcinoma (RCC) is a prevalent malignancy arising from the renal cortex, accounting for the majority of primary renal neoplasms.[1] Its global impact is over 400,000 new cases and 170,000 deaths reported annually.[2] Approximately 16% of RCC cases are diagnosed at metastatic stage.[3] Immunotherapy and targeted molecular therapy, has emerged as a promising approach for managing metastatic RCC, guided by disease burden and risk factors.[3] Previously, immunotherapy with interleukin-2 (IL-2) or interferon alpha (IFN-α) occupied a leading position due to their ability to stimulate interferons and natural killer cells.[4] In particular, IFN-α activates the immune system to recognize and fight cancer cells, including metastatic renal cell carcinoma.[5] However, new generation agents such as vascular endothelial growth factor (VEGF) inhibitors and immune checkpoint inhibitors (ICIs) have replaced IL-2 and IFN-α due to better tolerability and survival rates.[5,6] However, the challenge of choosing the most appropriate treatment remains after using these powerful options. Subsequent drug selection should be carefully considered, as the disease progresses and becomes more complex to manage.

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In recent times, rechallenge with immunotherapy has shown promise in melanoma and lung cancer, with ongoing clinical investigations in metastatic RCC.[7-9] This therapeutic approach is particularly interesting in Turkey, where reimbursement conditions favor the use of interferon as first-line therapy, and new generation immunotherapy agents such as Nivolumab are offered as third- or fourth-line treatment options. This unique scenario mimics immunotherapy rechallenge for these patients.

On the other hand, Type-1 interferons have recently gained attention in cancer immunotherapy. In particular, the activation of the STING pathway regulates immune responses, promoting anti-cancer effects and stimulating spontaneous T-cell responses.[10] In the view of such information, the present study aims to evaluate the effectiveness of repeat immunotherapy in patients previously treated with interferon for metastatic RCC.

Methods

Key eligibility criterias included metastatic RCC with clear cell histology, age ≥18 years, at least 2 months of interferon therapy in first-line, subsequent anti-VEGF therapy in second or third-line, and at least 2 subsequent dose of nivolumab. Demographic data, International Metastatic RCC Database Consortium (IMDC) risk scores, pre-treatment laboratory findings, and previous treatment lines were reviewed retrospectively. The primary outcome of the study was to reveal the overall survival (OS) and progression-free survival (PFS) rates and associated factors in immunotherapy re-administration RCC patients. Approval for the study was obtained from the local Ethics Committee.

Statistical Analysis

Statistical analyses were performed using IBM® SPSS software version 28. Descriptive statistics were presented as frequency (percent), mean±SD, or median (min-max). Survival estimates were calculated with the Kaplan-Meier method. The time from initiation of nivolumab to death from any cause and to progression was defined as OS and PFS, respectively. The log-rank test was used to identify the independent effects on survival. An overall type-1 error level was used to infer statistical significance.

Results

The mean age of the 54 patients (77.8% men) included in the study was 63.6±10.6 years, and 25 (46.3%) of the patients were over 65. The IMDC risk group was favorable in 16 (29.6%) patients, intermediate in 32 (59.3%), and poor in 6 (11.1%) patients. Prior to therapy, the mean hemoglobin level was 11.7±2.2 g/dl, the corrected calcium level was 9.6±0.78 mg/dl, the median neutrophil-to-lymphocyte ratio was 2.3 (0.2-21.4), and the median platelet-to-lymphocyte ratio was 155.3 (31.3-1365). In the first-line treatment, all patients received IFN-α, and in the second line, half received pazopanib and half received sunitinib. Seventy percent (38/54) of patients in the third line and 100% (16/16) of patients in the fourth line received nivolumab therapy. The median number of nivolumab cure was 16.5 (2-107) (Table 1).

During a median follow-up of 23.8 (1.7-74.8) months, cancer progressed in 37 (68.5%) patients and 31 (54.7%) patients died. The median OS was 25.3 (95% CI: 22.3-28.3) months and median PFS was 9.7 (95% CI: 4.8-14.6) months. The 2-year and 5-year OS rates were 57.8% (95% CI: 44.3-71.3) and 33.8% (95% CI: 19.1-48.5), respectively (Fig. 1). The 2-year and 5-year PFS rates were 34.3% (95% CI: 21.4-47.2) and 29.4% (95% CI: 16.7-42.1), respectively (Fig. 2). No significant relationships were found between OS and sex (p=0.585), age (< vs. ≥65 years, p=0.98), IMDC risk groups

Table 1. Patient characteristics

Characteristics	Frequency (%), n=54
Male sex	42 (77.8)
Age, mean±SD, years	63.6±10.6
<65 years	29 (53.7)
≥65 years	25 (46.3)
IMDC risk group	
Favorable	16 (29.6)
Intermediate	32 (59.3)
Poor	6 (11.1)
Pre-treatment laboratory findings	
Hemoglobin, mean±SD, g/dl	11.7±2.2
Corrected calcium, mean±SD, mg/dl	9.6±0.78
NLR, median (min-max)	2.3 (0.2-21.4)
PLR, median (min-max)	155.3 (31.3-1365)
Second-line treatment	
Pazopanib	27 (50)
Sunitinib	27 (50)
Third-line treatment	
Nivolumab	38 (70.4)
Axitinib	10 (18.5)
Sunitinib	2 (3.7)
Everolimus	2 (3.7)
Pazopanib	1 (1.9)
Gemcitabine and carboplatin	1 (1.9)
Fourth-line treatment, n=16	
Nivolumab	16 (100)
Nivolumab cure, median (min-max)	16.5 (2-107)

IMDC: International metastatic renal cell carcinoma database consortium; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SD: Standard deviation.
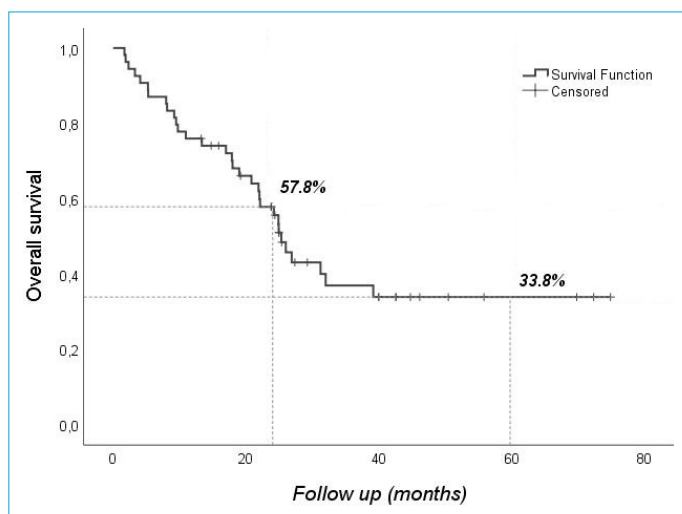
Figure 1. Overall survival rates.

Figure 2. Progression-free survival rates.

(p=0.39), second-line treatment (pazopanib vs. sunitinib, p=0.425) or nivolumab line (III vs. IV, p=0.249). PFS was consistent with OS in this sense (Table 2).

Discussion

Tertiary management of metastatic RCC is challenging due to scarcity of data. In recent years, many agents such as sorafenib, axitinib, cabozantinib, lenvatinib, and tivozanib have been investigated in advanced disease.[11-14] In the phase III TARGET trial, the VEGF inhibitor sorafenib showed a considerable increase in PFS compared to placebo, but no significant improvement in OS.[11] Similarly, axitinib, another VEGF inhibitor, improved PFS compared
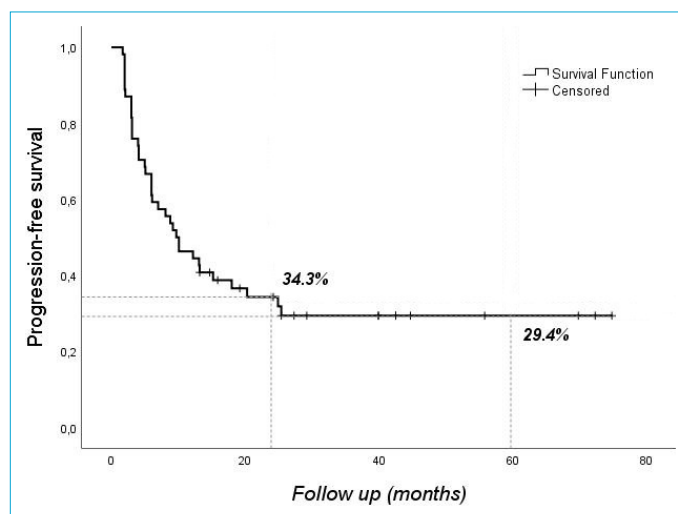
to sorafenib in the AXIS trial, although OS remained comparable between the two agents.[12] These findings highlight the necessity for more effective third-line alternatives for patients previously exposed to VEGF-targeted therapies. The combination of lenvatinib and everolimus has promising efficacy as a third-line treatment for RCC, with a median PFS of 14.6 months reported in a phase II study.[13] This combination presents a potential option for patients with prior exposure to VEGF or mTOR inhibitors. Tivozanib, another VEGF inhibitor, demonstrated improved PFS compared to sorafenib in the TIVO-3 trial. Nevertheless, akin to other VEGF inhibitors, tivozanib did not exhibit a significant difference in OS.[14]

Table 2. Overall survival and demographic and clinical parameters

Parameters	Median OS, months (95% CI)	p	Median PFS, months (95% CI)	p
Sex				
Male	24.9 (20.5-29.3)	0.585	9.7 (4.3-15.1)	0.421
Female	26 (14.6-37.3)		7 (2.3-11.6)	
Age				
<65 years	22.1 (13-31.2)	0.980	7 (2.1-11.9)	0.243
≥65 years	26 (23.2-28.7)		15.2 (0-30.5)	
IMDC risk group				
Favorable	31.2 (8.7-53.7)	0.390	10.1 (2.2-17.9)	0.837
Intermediate	26 (20.4-31.6)		7 (1.3-12.7)	
Poor	21.9 (6.7-37)		9.7 (4.8-14.6)	
Second-line treatment				
Pazopanib	22.1 (17.5-26.7)	0.425	8.1 (3.6-12.8)	0.064
Sunitinib	25.3 (15-35.6)		20.3 (1.6-39)	
Nivolumab line				
III	26 (18.5-33.4)	0.249	9.7 (3.5-15.9)	0.407
IV	18 (2.4-35.5)		8.8 (0.9-16.6)	

CI: confidence interval; IMDC: international metastatic renal cell carcinoma database consortium; OS: overall survival; PFS: progression-free survival.

The increasing adoption of the combination of immuno-therapy and anti-VEGF as initial treatments has influenced the choice of subsequent therapies in RCC.[15] This evolving treatment environment has led to complexity in decision-making for tertiary and subsequent treatments. Notably, the concept of rechallenging with ICIs has garnered sub-stantial interest as a prospective approach for patients with advanced RCC who have previously responded to initial treatment but experienced disease progression. Several studies reported promising results with immunotherapy re-challenge, demonstrating enduring responses and disease control in a subset of patients.[16,17] The objective response rates, ranging from 23% to 31%, suggest that re-treatment with ICIs may represent a viable option for selected pa-tients in the later stages. PFS rates in patients receiving sal-vage nivolumab/ipilimumab combination treatment was 4 month.[16] In the meta-analysis conducted by Papathanas-siou et al.,[18] the pooled PFS was 5.6 (4.1 to 7.8) months.

In our study, we concentrated on patients with a history of receiving IFN-α and anti-VEGF treatments and investigated the effectiveness of immunotherapy rechallenge in this specific cohort. The observed median PFS of 9.7 months in our study surpassed the previous data on immunotherapy rechallenge, implying a potential benefit of IFN-α in aug-menting immunotherapy response. The noteworthy abil-ity of IFN-α to modulate major histocompatibility complex (MHC) molecules on cancer cells is of particular interest, as heightened MHC expression enhances tumor antigen pre-sentation to T cells, thereby facilitating enhanced immune recognition and targeting of cancer cells.[19] Combination therapies involving IFN-α and ICIs have demonstrated promise in preclinical and clinical studies encompassing diverse cancer types, including melanoma and renal cell carcinoma. These findings suggest that such combinations may engender improved response rates and prolonged survival in comparison to ICIs administered alone.[20]

It is imperative to acknowledge the limitations in our study, including its retrospective nature and the relatively small sample size. Consequently, larger prospective studies are warranted to further corroborate the efficacy of immuno-therapy rechallenge in patients previously treated with in-terferon alfa and anti-VEGF therapies.

Conclusion

In conclusion, the management of metastatic RCC in the third-line remains a challenge, due to limited data. Immu-notherapy rechallenge has emerged for selected patients, and our study supports this approach in patients who pre-viously received interferon alpha and anti-VEGF. Further research is needed to elucidate the mechanisms underly-ing the potential synergy between IFN-α and ICIs, and to identify predictive biomarkers that may facilitate patient selection for this strategy.

References

1. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol. 2010; 7; 245-257.
2. Ljungberg B, Campbell SC, Choi HY, et al. The epidemiology of renal cell carcinoma. Eur Urol. 2011; 60; 615-621.
3. Leibovich BC, Lohse CM, Cheville JC, et al. Predicting Oncolog-ic Outcomes in Renal Cell Carcinoma After Surgery. Eur Urol. 2018; 73; 772-780.
4. Margolin K, Aronson FR, Sznol M, et al. Phase II studies of re-combinant human interleukin-4 in advanced renal cancer and malignant melanoma. J Immunother Emphasis Tumor Immu-nol. 1994; 15; 147-153.
5. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. N Engl J Med. 1998; 338: 1272-1278.
6. Sidaway P. New combination therapy for advanced-stage RCC. Nat Rev Clin Oncol. 2023; 20: 353.
7. Xu Z, Hao X, Yang K, et al. Immune checkpoint inhibitor rechal-lenge in advanced or metastatic non-small cell lung cancer: a retrospective cohort study. J Cancer Res Clin Oncol. 2022; 148: 3081-3089.
8. Zaremba A., Eggermont AMM, Robert C, et al. The concepts of rechallenge and retreatment with immune checkpoint block-ade in melanoma patients. Eur J Cancer. 2021; 155: 268-280.
9. Sammarco E, Manfredi F, Nuzzo A, et al. Immune Checkpoint Inhibitor Rechallenge in Renal Cell Carcinoma: Current Evi-dence and Future Directions. Cancers (Basel). 2023; 15: 3172.

10. Luo K, Li N, Ye W, Gao H, Luo X, Cheng B. Activation of Stimulation of Interferon Genes (STING) Signal and Cancer Immunotherapy. Molecules. 2022; 27: 4638.

11. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007; 356: 125-134.

12. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011; 378: 1931-1939.

13. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015; 16: 1473-1482.

14. Pal SK, Escudier BJ, Atkins MB, et al. Final Overall Survival Results from a Phase 3 Study to Compare Tivozanib to Sorafenib as Third- or Fourth-line Therapy in Subjects with Metastatic Renal Cell Carcinoma. Eur Urol. 2020; 78: 783-785.

15. Quhal F, Mori K, Bruchbacher A, et al. First-line Immunotherapy-based Combinations for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. Eur Urol Oncol. 2021; 4: 755-765.

16. Gul A, Stewart TF, Mantia CM, et al. Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors. J Clin Oncol. 2020; 38: 3088-3094.

17. Ravi P, Mantia C, Su C, et al. Evaluation of the Safety and Efficacy of Immunotherapy Rechallenge in Patients With Renal Cell Carcinoma. JAMA Oncol. 2020; 6: 1606-1610.

18. Papathanassiou M, Tamposis I, Exarchou-Kouveli KK, et al. Immune-based treatment re-challenge in renal cell carcinoma: A systematic review and meta-analysis. Front Oncol. 2022; 12: 996553.

19. Vidal P. Interferon α in cancer immunoediting: From elimination to escape. Scand J Immunol. 2020; 91: e12863.

20. Zhu S, Zhang T, Zheng L, et al. Combination strategies to maximize the benefits of cancer immunotherapy. J Hematol Oncol. 2021; 14: 156.