Editorial Commentary

Effectiveness of switch therapy from tyrosine kinase inhibitors to immune checkpoint inhibitors: the need for biomarkers to establish treatment strategies in patients with metastatic renal cell carcinoma

Yoshihiko Tasaki[1], Shuzo Hamamoto[2], Yoko Furukawa-Hibi[1], Takahiro Yasui[2]

[1]Department of Clinical Pharmaceutics, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan; [2]Department of Nephro-urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan

Correspondence to: Shuzo Hamamoto, MD, PhD. Department of Nephro-urology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan. Email: hamamo10@med.nagoya-cu.ac.jp.

Comment on: Grünwald V, Ivanyi P, Zschäbitz S, *et al*. Nivolumab Switch Maintenance Therapy After Tyrosine Kinase Inhibitor Induction in Metastatic Renal Cell Carcinoma: A Randomized Clinical Trial by the Interdisciplinary Working Group on Renal Tumors of the German Cancer Society (NIVOSWITCH; AIO-NZK-0116ass). Eur Urol 2023;84:571-8.

Keywords: Nivolumab; immune checkpoint inhibitor (ICI); tyrosine kinase inhibitor (TKI); renal cell carcinoma (RCC)

Submitted Dec 14, 2023. Accepted for publication Feb 21, 2024. Published online Apr 12, 2024.
doi: 10.21037/tau-23-647
View this article at: https://dx.doi.org/10.21037/tau-23-647

The estimated 5-year survival rate between 2013 and 2018 for advanced metastatic renal cell carcinoma (RCC) was approximately 13% (1), indicating that RCC is associated with poor survival. This situation has substantially changed in recent years with the approval of immune checkpoint inhibitors (ICIs). ICIs have played a revolutionary role in improving the overall and progression-free survival of patients with RCC (2-6). However, recently, there has been uncertainty regarding treatment strategies for RCC.

The standard first-line therapy for RCC consists of four regimens of ICI combination therapy and ICI plus tyrosine kinase inhibitor (TKI) therapy, including ipilimumab plus nivolumab, cabozantinib plus nivolumab, pembrolizumab plus lenvatinib, and pembrolizumab plus axitinib therapy (2-5). A large-scale clinical trial has shown that ICI combination therapy and ICI plus TKI combination therapy lead to better clinical outcomes than sunitinib and everolimus (2-5). Patients not eligible for ICI have used TKI monotherapy. While these therapies are selected based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category, histological subtype, and patient condition (7,8), the optimum treatment choice is not clearly defined and is left to the physician's discretion. From second-line therapy and beyond, TKI monotherapy (cabozantinib and axitinib) and nivolumab monotherapy are used in sequence (7,8). However, consistent with the selection of first-line therapy, treatment choices in second-line settings for subsequent TKI and nivolumab monotherapy have not been clarified. Therefore, RCC has no clear treatment strategy, encompassing first-line, second-line, and subsequent treatments, leaving uncertainty regarding the choice between TKIs or ICIs and the indications of combination therapy.

In this context, Grünwald *et al.* (9) conducted a key investigation in which patients with RCC who responded to TKIs (sunitinib and pazopanib) as first-line therapy were randomly divided into two groups: continued TKI treatment and a switch to nivolumab maintenance treatment. In an open-label phase 2 trial, Grünwald *et al.* investigated whether switching to nivolumab would be effective for patients with RCC who responded to TKIs. The overall response rate was significantly different between patients who continued TKI treatment and those who switched to nivolumab maintenance treatment: complete

response, 8.7% *vs.* 0.0%; partial response, 44.0% *vs.* 20.0%; stable disease, 26.0% *vs.* 24.0%; and disease progression, 13.0% *vs.* 48.0%. While the median overall survival did not differ between the continued TKI treatment group and the switched to nivolumab maintenance treatment group (43.8 months *vs.* not reached), the median progression free survival of patients who continued TKI treatment was significantly longer than that of patients who switched to nivolumab maintenance treatment (11.9 *vs.* 3.0 months). Therefore, Grünwald *et al.* concluded that the treatment of patients receiving TKI as first-line therapy should not be changed during the course of their treatment.

This study had three limitations. First, when stratifying patients, analyses based on gene expression may be inadequate. The combination of ICI and TKI is a rational therapy in terms of immunology (10). Angiogenic factors, such as vascular endothelial, platelet-derived, and hepatocyte growth factors, are involved in the suppression of anti-tumor immunity by promoting the infiltration of regulatory T cells and increasing the expression of programmed death receptor-1 and cytotoxic T-lymphocyte-associated protein 4 (10). Therefore, treatment with TKI is expected to activate anti-tumor immunity. However, in the current study, switch therapy did not show superior clinical outcomes. Further, the outcomes of this study might have been influenced by patient selection bias, as stated by Grünwald *et al.* Second, since ICI combination therapy and ICI plus TKI therapy are used as first-line therapies for patients with RCC, few patients receive TKI monotherapy as the first-line therapy. Only patients with RCC who cannot tolerate ICI therapy may receive TKI monotherapy, such as pazopanib, sunitinib, and cabozantinib, as the first-line therapy (7,8). Third, because only a small number of patients participated in this study, the validity of switching maintenance therapy may be insufficient.

Nonetheless, several important points have been made in this study. An important aspect of this study is that it is the first to report on switch maintenance therapy. Next, it demonstrated the possibility of stratifying patients who should be treated aggressively with TKIs or ICIs. In order to address the problem of patients receiving ICIs and TKIs, identifying biomarkers that predict therapeutic efficacy is necessary.

Currently, various studies are being actively conducted to investigate biomarkers for the therapeutic efficacy of ICI using genetic expression/mutation, blood parameters, and adverse effects, as well as to discover prognostic markers for RCC (11-22). For instance, expression levels of cyclin-dependent kinase 5 and 6, which play important roles in the cell cycle, are associated with the efficacy of ICIs (11,12). Wang *et al.* showed that elevated RUNX3 expression levels in tumor tissue was associated with poor ICI efficacy (13). Tumor mutational burden plays an important role in the efficacy of ICIs (14,15). Our previous study reported that hemoglobin and neutrophil levels may be biomarkers for predicting the effectiveness of ipilimumab plus nivolumab therapy in patients with RCC (16). Several studies showed that the expression of programmed death-ligand 1 (PD-L1) may be also associated with better clinical outcomes in patients with RCC receiving ICI (20-22). Although Grünwald *et al.* examined the association between PD-L1 expression and clinical outcomes, previous study has not revealed the relevance of PD-L1 expression in RCC (9). As Grünwald *et al.* discussed, this may be due to the variation in the proportion of patients with PD-L1 positivity between those who continued TKI treatment and those who switched to nivolumab maintenance treatment. These results make it difficult to determine the effectiveness of switching to nivolumab maintenance therapy.

Additionally, several studies have examined biomarkers for the therapeutic efficacy of TKI therapy (23-25). They showed that hepatocyte growth factor and angiogenesis levels might be associated with improved clinical survival (23,24). Furthermore, hemoglobin levels are related to the effectiveness of TKI therapy in patients with RCC (25).

Despite many studies evaluating biomarkers, there is no unified view on using biomarkers in clinical practice. Currently, biomarkers that can stratify patients with RCC to either TKI or ICI monotherapy, including combination therapy, should be established, and treatment strategies should be developed. Large-scale studies assessing biomarkers for therapeutic efficacy are needed to establish treatment strategies for RCC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article has undergone external peer review.

Peer Review File: Available at https://tau.amegroups.com/

article/view/10.21037/tau-23-647/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-647/coif). S.H. receives honoraria for lectures from Takeda Pharmaceuticals, Boston Scientific Japan, Takai and Olympus. T.Y. receives honoraria for lectures from Takeda Pharmaceuticals, Boston Scientific Japan, Asuteras, Kissei Pharmacy, Kyorin Pharmacy, Janssen Pharma, Bayer, Merck Biopharma, Olympus, Eisai, Noippon-shinyaku and MSD. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Motzer RJ, McDermott DF, Escudier B, et al. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. Cancer 2022;128:2085-97.
3. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2021;384:829-41.
4. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med 2021;384:1289-300.
5. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1116-27.
6. Motzer RJ, Escudier B, George S, et al. Nivolumab versus everolimus in patients with advanced renal cell carcinoma: Updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. Cancer 2020;126:4156-67.
7. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20:71-90.
8. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. Eur Urol 2022;82:399-410.
9. Grünwald V, Ivanyi P, Zschäbitz S, et al. Nivolumab Switch Maintenance Therapy After Tyrosine Kinase Inhibitor Induction in Metastatic Renal Cell Carcinoma: A Randomized Clinical Trial by the Interdisciplinary Working Group on Renal Tumors of the German Cancer Society (NIVOSWITCH; AIO-NZK-0116ass). Eur Urol 2023;84:571-8.
10. Guillaume Z, Auvray M, Vano Y, et al. Renal Carcinoma and Angiogenesis: Therapeutic Target and Biomarkers of Response in Current Therapies. Cancers (Basel) 2022;14:6167.
11. Xu X, Wang Y, Chen Z, et al. Favorable Immunotherapy Plus Tyrosine Kinase Inhibition Outcome of Renal Cell Carcinoma Patients with Low CDK5 Expression. Cancer Res Treat 2023;55:1321-36.
12. Wang J, Zhang S, Wang Y, et al. The prognostic significance of CDK6 expression in renal cell carcinoma treated by immune checkpoint plus tyrosine kinase inhibition. Scand J Immunol 2023;98:e13304.
13. Wang J, Zhang S, Wang Y, et al. RUNX3 pathway signature predicts clinical benefits of immune checkpoint inhibition plus tyrosine kinase inhibition in advanced renal cell carcinoma. BMC Urol 2024;24:8.
14. Chan TA, Yarchoan M, Jaffee E, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Ann Oncol 2019;30:44-56.
15. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med 2017;377:2500-1.
16. Tomiyama N, Tasaki Y, Hamamoto S, et al. Hemoglobin and neutrophil levels stratified according to International Metastatic Renal Cell Carcinoma Database Consortium risk predict the effectiveness of ipilimumab plus nivolumab in patients with advanced metastatic renal cell carcinoma. Int J Urol 2023;30:754-61.
17. Chen X, Meng F, Jiang R. Neutrophil-to-Lymphocyte Ratio as a Prognostic Biomarker for Patients With Metastatic Renal Cell Carcinoma Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. Front Oncol 2021;11:746976.

18. Tasaki Y, Sugiyama Y, Hamamoto S, et al. Eosinophil may be a predictor of immune-related adverse events induced by different immune checkpoint inhibitor types: A retrospective multidisciplinary study. Cancer Med 2023;12:21666-79.
19. Tasaki Y, Hamamoto S, Sugiyama Y, et al. Elevated eosinophils proportion as predictor of immune-related adverse events after ipilimumab and nivolumab treatment of advanced and metastatic renal cell carcinoma. Int J Urol 2023;30:866-74.
20. McDermott DF, Lee JL, Ziobro M, et al. Open-Label, Single-Arm, Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Non-Clear Cell Renal Cell Carcinoma. J Clin Oncol 2021;39:1029-39.
21. Atkins MB, Jegede OA, Haas NB, et al. Phase II Study of Nivolumab and Salvage Nivolumab/Ipilimumab in Treatment-Naive Patients With Advanced Clear Cell Renal Cell Carcinoma (HCRN GU16-260-Cohort A). J Clin Oncol 2022;40:2913-23.
22. Denize T, Hou Y, Pignon JC, et al. Transcriptomic Correlates of Tumor Cell PD-L1 Expression and Response to Nivolumab Monotherapy in Metastatic Clear Cell Renal Cell Carcinoma. Clin Cancer Res 2022;28:4045-55.
23. Nakaigawa N, Tomita Y, Tamada S, et al. Final efficacy and safety results and biomarker analysis of a phase 2 study of cabozantinib in Japanese patients with advanced renal cell carcinoma. Int J Clin Oncol 2023;28:416-26.
24. Denize T, Farah S, Cimadamore A, et al. Biomarkers of Angiogenesis and Clinical Outcomes to Cabozantinib and Everolimus in Patients with Metastatic Renal Cell Carcinoma from the Phase III METEOR Trial. Clin Cancer Res 2022;28:748-55.
25. Bilir C, Yıldız İ, Bilici A, et al. Is Change in Hemoglobin Level a Predictive Biomarker of Tyrosine Kinase Efficacy in Metastatic Renal Cell Carcinoma? A Turkish Oncology Group Study. Cancer Invest 2017;35:248-55.

Cite this article as: Tasaki Y, Hamamoto S, Furukawa-Hibi Y, Yasui T. Effectiveness of switch therapy from tyrosine kinase inhibitors to immune checkpoint inhibitors: the need for biomarkers to establish treatment strategies in patients with metastatic renal cell carcinoma. Transl Androl Urol 2024;13(4):631-634. doi: 10.21037/tau-23-647

