Opinion

Proposal of "cyclic therapy", a novel treatment strategy with targeted agents for advanced renal cell carcinoma

Masahiro Nozawa, Hirotsugu Uemura

Department of Urology, Kinki University Faculty of Medicine,377-2 Ohno-higashi, Osaka-sayama, 589-8511, Japan
Correspondence to: Masahiro Nozawa, MD, PhD. Department of Urology, Kinki University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Email: nozawa06@med.kindai.ac.jp.

Abstract: The number of molecular targeted agents for advanced renal cell carcinoma (RCC) has gradually increased, but evidence on the optimal order of selection for such agents has not yet caught up with this trend. In addition, timing of switching molecular targeted drugs may also become an important issue for controlling the disease as types of these drugs grow in number. Based on the fact that the efficacy of a rechallenge of the drug previously used suggests the recovery of the sensitivity, a cyclic therapy in which drugs are changed before exacerbation to repeatedly administer several drugs in a rotated manner, may also be an effective sequential therapy.

Keywords: Cyclic therapy; sequential therapy; rechallenge; renal cell carcinoma (RCC); targeted therapy

Submitted Oct 11, 2013. Accepted for publication Nov 20, 2013.
doi: 10.3978/j.issn.2223-4683.2013.12.03
Scan to your mobile device or view this article at: http://www.amepc.org/tau/article/view/3126/4041

Current status and challenges of sequential therapy in advanced renal cell carcinoma

At present, it is evident that complete remission of metastatic renal cell carcinoma (mRCC) can be hardly expected through administration of an existing molecular targeted agent alone (1-10). On the other hand, simultaneous combination therapy with multiple molecular targeted agents may not be realistic in terms of tolerance (11-14). Therefore, the goal of current medical treatment for advanced RCC should be to aim for maximal extension of survival by sequentially administering individual drugs, while maintaining as high quality of life (QOL) as possible. For this purpose, recommended drugs for each setting have been proposed in various guidelines based on evidence obtained (15,16).

Unfortunately, valuable evidence on which drug selection for conducting sequential therapy can be absolutely defined has not been fully collected. For example, when sunitinib is used in a patient as first-line therapy, everolimus or axitinib is usually considered as the option for the second-line therapy after the patient develops resistance to sunitinib. However, there has been no evidence demonstrating which of these two drugs is superior to the other.

In addition, even when superiority of either drug is shown, drug efficacy from the third-line treatment and thereafter may be reversed, or no difference may be observed in the final overall survival (OS). In fact, in the AXIS trial, although superiority of axitinib to sorafenib as the second-line therapy was shown from the viewpoint of progression-free survival (PFS), there was no significant difference in OS between the two groups (2). These results suggest that, because there are other effective agents that can be administered at or after the third-line therapy, the final treatment outcome may become almost constant regardless of the order of drugs used, when full use of these alternative drugs can be skillfully made. In other words, a proposition is raised: how meaningful is it, from the viewpoint of OS, true benefit for the patients, to determine the order of drugs used by comparing PFS for individual drugs?

Currently, only for the first-line therapy, at least three treatment effective options, sunitinib, pazopanib, and a combined therapy of bevacizumab/IFN, are present for favorable- and intermediate-prognosis patients. When possible drug combinations for sequential treatment as the second-, third-, or fourth-line therapy are considered,

© Translational Andrology and Urology. All rights reserved.

conducting clinical trials to determine merits and demerits of all the drug combinations is not feasible, because the patterns of combination therapy increase at an exponential rate. Eventually, it may be almost impossible to build up high-quality evidence to establish the most effective sequential therapy when OS is used as the primary endpoint.

The meaning of the efficacy of rechallenge

We have already reported an outcome of rechallenge with sorafenib in our institute (17). In the study, patients were administered with first sorafenib with a median PFS of 5.7 months. Subsequently, these patients experienced treatments with sunitinib and everolimus, and after a 7.6-month median interval from the initial sorafenib challenge, they were rechallenged with sorafenib. The median PFS on the rechallenge was 5.4 months. Thus, the outcome of the sorafenib rechallenge was comparable to that of the first with sorafenib. For sunitinib, the effect of rechallenge was similarly investigated (18). These results suggest the presence of a mechanism in which, at least for sorafenib and sunitinib, sensitivity to these drugs can be regained by providing a given period of time without treatment, even after resistance to these two drugs has developed. If the mechanism can be universally applied to other targeted agents, it will further broaden options to select drugs used in sequential treatment.

Unlike the era in which only sorafenib and sunitinib were available soon after the approval of these first molecular targeted drugs, in the current situation, in which seven molecular targeted agents can be used, there may possibly be doubts on the importance of rechallenge therapy. However, in actual clinical settings, drugs should be selected based not only on prognostic factors and previous history of treatment shown in algorithms in guidelines, but also patient's age, performance status, functions of various organs, as well as concomitant diseases and profiles of adverse events for the drugs should be fully considered. Therefore, although seven drug options are potentially available for the patient, drugs that can actually be administered to an individual patient for a long time may be limited in many cases, depending on comorbidity and/or development of adverse events. In these cases, the following sequential therapy can be applied: a drug mainly used in the treatment should be rechallenged, while other drugs are not administered more than necessary for a prolonged period, and used as a relief during the period between the first challenge and rechallenge with the main drug. Therefore, an implication suggested by the efficacy of rechallenge was that it proposed a rationale for discussion of the timing of switching drugs for advanced RCC.

Timing of switching drugs

It has been reported that clear cell carcinoma, which accounts for approximately 80% of RCC, has heterogeneous genetic background depending on primary or metastatic focus, or site within a primary focus (19,20). Differences in genetic background suggest that sensitivity to drugs may be also varied. It is not a rare case in which responsiveness to a drug is significantly different between primary and metastatic foci, or a metastatic focus tends to shrink while other foci inversely show a trend to enlargement. One of the reasons for these phenomena may be the heterogeneity of gene mutation in these cancer cells. In that case, it is expected that simultaneous combination therapy with multiple drugs that target different molecules would show excellent anti-cancer effect, but this is unfortunately not realistic, at least in terms of tolerance to combined therapy with existing molecular targeted drugs. Consequently, there is no other way but to use several drugs by sequentially switching them. However, if a patient deteriorates instead of achieving complete remission, it means that the tumor was initially sensitive to a drug used but later developed resistance to the drug during treatment. In other words, in the course of therapy with continuous administration of a single drug, sensitivity of the tumor to the drug may be gradually decreased as a whole.

On the other hand, the efficacy of rechallenge suggests that no exposure to the drug during a given period of time may cause regaining of tumor sensitivity to the drug. When hypothesizing that some sensitivity can be restored by introducing a non-exposure period, additional anti-tumor effect can be expected by divided treatment with non-exposure periods through drug interruption, compared to continuous administration of the drug until sensitivity is lost. We will simulate a sequential therapy by applying this hypothesis. Treatment regimen 1 is a conventional sequential switch therapy in which three drugs are administered until the sensitivity of each drug is decreased to zero. By contrast, in treatment regimen 2, a drug is administered over divided dose periods by shortening single dosing duration and inserting other drugs to the non-exposure period. The latter method can not only add anti-tumor effect as sensitivity is regained, but also maintain sensitivity of the tumor to each

© Translational Andrology and Urology. All rights reserved.

drug, showing a potential for continuous treatment. In addition, in the latter regimen, no non-treatment period for cancer is present, because other drugs are administered during the non-exposure period of the main drug, which would otherwise be a non-treatment period if a single drug were used. It can be said that this dosing regimen works only in today's treatments of RCC, where a relatively long prognosis is expected because many effective drugs are available.

Proposal of "cyclic therapy"

An ideal drug selection would of course be a tailor-made treatment based on biological characteristics of a patient and his/her tumor. However, predictive markers of therapeutic effects to determine the optimal drug for the cancer in a patient before treatment have not yet established. In addition, under present circumstances, even the evidence necessary to determine an order of administration of drugs is insufficient, as mentioned above.

Seven different drugs are now available for RCC, after approval of axitinib. It is highly possible that more new drugs will be developed in the future. In a sequential therapy, it may be difficult to administer all drugs to be used in the natural course of cancer if each of these drugs is continued until disease deterioration. In other words, there may be drugs that are not administered to the patient before end of treatment. In that case, the possibility cannot be denied that drugs that were sixth or seventh on a waiting list could have been the most beneficial agent for the patient. To avoid such a misfortune, the dosing regimen described above would be useful. For example, drugs could be evaluated based on the following criteria at the stage after administering all the drugs within the first treatment cycle: I. the most beneficial drug; II. drugs with excellent anti-tumor effect but poor tolerance; III. drugs with intermediate anti-tumor effect and tolerance; IV. drugs showing some anti-tumor effect but leading to unacceptable adverse event(s); and V. drugs not showing any anti-tumor effect. Based on the preliminary evaluation, drugs that met criteria IV and V are withdrawn from treatment, and only drugs that met criteria I, II, and III are used from the second cycle: Drug I is mainly used, and a non-exposure period is set after a certain treatment period with Drug I. Drugs II and III are inserted between the first treatment and rechallenge with Drug I. This "cyclic therapy" with these three different drugs would be repeated. Apart from whether this model is an ideal sequential therapy or not, it may be an idea worth considering as a method to achieve a therapeutic goal for advanced RCC aiming to maximally extend survival while maintaining as high QOL as possible.

Conclusions

New drugs effective for RCC could be continuously developed in the future. Evidence cannot always indicate all the answers to the many questions in drug selection. Although a tailor-made therapy based on biological characteristics of a patient and his/her tumor would be ideal, no markers for predicting effects of treatment have been discovered to date. In this context, we must always explore treatment methods that can lead to as much benefit for patients as possible. Evidently, our goal is not to seek a means to continuously administer a single agent for as long as possible. We should play a role in making full use of the treatment modalities currently available and considering and devising ways to obtain the optimal outcome.

Acknowledgements

None.

Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

References

1. Grünwald V, Karakiewicz PI, Bavbek SE, et al. An international expanded-access programme of everolimus: addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy. Eur J Cancer 2012;48:324-32.
2. 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;378:1931-9.
3. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. Cancer 2010;116:1272-80.
4. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer

© Translational Andrology and Urology. All rights reserved.

global evaluation trial. J Clin Oncol 2009;27:3312-8.
5. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584-90.
6. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009;10:757-63.
7. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.
8. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-81.
9. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125-34.
10. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.
11. Patel PH, Senico PL, Curiel RE, et al. Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma. Clin Genitourin Cancer 2009;7:24-7.
12. Négrier S, Gravis G, Pérol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol 2011;12:673-80.
13. Hainsworth JD, Waterhouse DM, Penley WC, et al. Sorafenib and everolimus in advanced clear cell renal carcinoma: a phase I/II trial of the SCRI Oncology Research Consortium. Cancer Invest 2013;31:323-9.
14. Molina AM, Feldman DR, Voss MH, et al. Phase 1 trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma. Cancer 2012;118:1868-76.
15. Escudier B, Eisen T, Porta C, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii65-71.
16. NCCN Guidelines Version 1.2013. Kidney Cancer. Available online: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf (accessed October 11, 2013).
17. Nozawa M, Yamamoto Y, Minami T, et al. Sorafenib rechallenge in patients with metastatic renal cell carcinoma. BJU Int 2012;110:E228-34.
18. Zama IN, Hutson TE, Elson P, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer 2010;116:5400-6.
19. Staller P. Genetic heterogeneity and chromatin modifiers in renal clear cell carcinoma. Future Oncol 2010;6:897-900.
20. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883-92.

Cite this article as: Nozawa M, Uemura H. Proposal of "cyclic therapy", a novel treatment strategy with targeted agents for advanced renal cell carcinoma. Transl Androl Urol 2013;2(4):324-327. doi: 10.3978/j.issn.2223-4683.2013.12.03

© Translational Andrology and Urology. All rights reserved.