Sequential medical therapy in renal carcinoma

Raffaele Ratta[1], Aristotelis Bamias[2]

Abstract
Renal cell carcinoma (RCC) is the ninth most common cancer in humans. In the last decade, a better understanding of the molecular mechanisms underlying tumorigenesis, angiogenesis, cell growth and proliferation, and the discovery of molecular alterations involved in RCC pathogenesis, have led to the identification of molecular targets of great clinical interest that have revolutionized the treatment of metastatic RCC (mRCC). Sunitinib, pazopanib and bevacizumab plus interferon-alpha remain the standard first-line treatments: these agents have significantly improved prognosis in mRCC. Everolimus, axitinib and sorafenib have demonstrated significant efficacy as second-line therapies. Nivolumab and cabozantinib are the most promising new-generation agents in the treatment of RCC. All of these agents, given in sequence, have extended life expectancy of RCC patients from 13 months in the cytokine era to over 20 months. Despite this improvement, it is not easy to establish the right sequence in which to administered different agents because there aren't yet ways to identify or select patients likely to benefit or those who could be resistant to specific drugs. In this review we present clinical data on the sequential treatment in RCC and discuss key factors that need to be considered when physicians make treatment decisions for individual patients.

Key words: renal cell carcinoma, immunotherapy, m-TOR inhibitors, tyrosine kinase inhibitors

Introduction

Renal cell carcinoma (RCC) is the ninth most common human cancer. In the United States about 62,700 new cases are expected to occur in 2016, associated with more than 14,240 deaths [1]. Approximately 25% of patients with RCC present with locally advanced or metastatic disease at diagnosis, and about 20-40% of patients with confined primary tumor will eventually develop metastatic disease [2, 3].

Until 2005, interleukin-2 (IL-2) and interferon-alpha (IFN-α) were the standards of care in the treatment of metastatic RCC (mRCC). These therapies were associated with few durable responses and considerable dose-limiting toxicities [4]. More recently, a better understanding of the molecular mechanisms underlying tumorigenesis, angiogenesis, cell growth and proliferation, and the discovery of the molecular alterations involved in RCC pathogenesis, have allowed the identification of several molecular targets of great therapeutic interest [5-8]. These include the vascular endothelial growth factor (VEGF) and its receptors (VEGFRs), the mammalian target of rapamycin (mTOR) signaling pathway, the hypoxia inducible factors (HIFs) and the fibroblast growth factor (FGF) and its receptor (FGFR). Identification of these molecular targets has led to the development of systemic treatments that have been incorporated into the treatment paradigm in mRCC, such as the humanized anti-VEGF monoclonal antibody bevacizumab in combination with IFN-α, the multitargeted tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, pazopanib and axitinib, and two kinase inhibitors of mTOR, temsirolimus and everolimus. The introduction of these agents has changed the treatment landscape and prognosis of mRCC patients; they have been associated with progression-free survival (PFS) and overall survival (OS) benefit, while very long-term disease control has also been re-

[1]Medical Oncology Department,
University Campus Bio-Medico, Rome, Italy.
[2]Department of Clinical Therapeutics, School of Medicine,
National & Kapodistrian University of Athens, Athens, Greece.
Correspondence to:
Aristotelis Bamias, MD
Dept. of Clinical Therapeutics,
Alexandra Hospital Ave Vas. Sofias 80, 115 28 Athens, Greece.
Phone:+30 2132162845 – Fax: +30 2132162511
E-mail: abamias@med.uoa.gr
CANCER BREAKING NEWS 2016;4(3):6-11
DOI: 10.19156/cbn.2016.0022

ported [9]. Nevertheless, resistance to first-line treatment occurs after a median time of 8-11 months, necessitating a change of treatment in the majority of cases [10, 11]. Most of the approved targeted therapies have shown efficacy in relapsed disease. Therefore, an important consideration is the sequence in which these agents should be used. The sequencing question becomes of primary importance when multiple treatments are developed in a short period of time or new drugs are licensed before others have a definite place in the therapeutic armamentarium; this is also complicated by the lack of studies directly comparing new agents as well as uncertainty around the association of disease progression with RECIST criteria and the need for change in therapy. In this article, we focus on the sequential treatment of mRCC and discuss the main factors that physicians need to take into account when making therapeutic decisions.

First-line therapy in mRCC

Several new anti-VEGF drugs have been approved for first-line treatment in mRCC. These agents have improved patient outcomes compared with the previous cytokines-based standard of care (Table 1).

Current evidence-based guidelines [3] recommend three agents as first-line treatment for patients with good-intermediate risk according to Memorial Sloan Kettering Cancer Center (MSKCC) risk groups: bevacizumab (combined with IFN-α), sunitinib and pazopanib. First-line temsirolimus has demonstrated activity in patients with poor prognosis [12]. Bevacizumab combined with IFN-α significantly improved PFS compared with IFN-α alone in mRCC [13]. Due to the need for frequent hospital visits associated with this combination and the toxicity of IFN-α, orally-administered sunitinib and pazopanib have become more popular in everyday practice.

Sunitinib is an oral, small-molecule, multi-targeted receptor TKI that was approved for first-line treatment of RCC based on data from a phase III trial showing its superiority over IFN-α [14]. In this trial, 750 patients with previously untreated mRCC were enrolled and randomized to receive oral sunitinib (50 mg once daily for 4 weeks, followed by 2 weeks' rest) or subcutaneous IFN-α (9 MU three times weekly). Sunitinib significantly improved PFS compared with IFN-α (11 *vs* 5 months, hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.32-0.54; p<0.001). Sunitinib was also associated with a higher objective response rate (ORR) (31% *vs* 6%; p<0.001). In general, patients treated with sunitinib reported significantly better quality of life than those in the IFN-α group (p<0.001).

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, platelet-derived growth factor receptor (PDGFR) and c-Kit; it was first tested in a randomized placebo-controlled phase III trial, with 54% treatment-naïve and 46% cytokine pre-treated patients [15, 16]. In this study, median PFS was significantly prolonged in pazopanib recipients compared with placebo in the overall study population (9.2 *vs* 4.2 months, HR 0.46, 95%CI 0.34-0.62; p<0.0001), treatment-naïve patients (11.1 *vs* 2.8 months, HR 0.40, 95%CI 0.27-0.60; p<0.0001), and cytokine-pretreated patients (7.4 *vs* 4.2 months, HR 0.54, 95%CI 0.35-0.84; p<0.001). The ORR was 30% with pazopanib compared with 3% with placebo. The most common adverse events (AEs) were diarrhea, hypertension, nausea, anorexia, vomiting and hair color changes. Pazopanib was compared head-to-head with sunitinib in a randomized non-inferiority trial in the first-line setting (COMPARZ trial) [17]. This study showed that pazopanib was non-inferior to sunitinib with respect to PFS (HR for progression of disease or death from any cause 1.05, 95%CI 0.90-1.22) (the predefined non-inferiority margin was upper bound of the 95%CI <1.25). OS was similar in patients treated with either of the two agents. Sunitinib *versus* pazopanib recipients had a higher incidence of fatigue (63% *vs* 55%), hand-foot syndrome (50% *vs* 29%) and thrombocytopenia (78% *vs* 41%), while patients treated with pazopanib had a higher incidence of increased alanine aminotransferase levels (60% *vs* 43% with sunitinib). A crossover trial (PISCES) was designed to assess patients' preference for pazopanib *versus* sunitinib [18];

Table 1. Treatment options for first-line therapy of renal cell carcinoma (evidence levels according to ESMO Clinical Practice Guidelines 2014).

Risk group (MSKCC)	Standard treatments	Optional treatments
Good or intermediate	Sunitinib (I, A) Pazopanib (I, A) Bevacizumab + interferon-α (I, A)	High-dose interleukin-2 (III, C) Sorafenib (II, B) Bevacizumab + low-dose interferon-α (III, B)
Poor	Temsirolimus (II, A)	Sunitinib (II, B) Sorafenib (III, B)

MSKCC: Memorial Sloan Kettering Cancer Center

patients with treatment-naïve mRCC were randomized to sequential use of pazopanib for 10 weeks followed by sunitinib for 10 weeks, or vice versa, with a 2-week washout period between treatments. At 22 weeks, significantly more patients preferred pazopanib (70%) over sunitinib (22%), while 8% did not have any preference. These findings underline the importance of a detailed discussion of different toxicity profiles with patients in order to make the appropriate treatment choices.

The superiority of anti-VEGFR therapy as initial treatment in mRCC over mTOR inhibition was established by the RECORD-3 trial. In this phase II study, patients were randomized to receive first-line everolimus followed by sunitinib at disease progression or sunitinib in first-line followed by everolimus [19]. The primary endpoint of non-inferiority was not met: median PFS was 7.9 months in patients treated with first-line everolimus compared with 10.7 months in those who had first-line sunitinib; corresponding values for median combined PFS were 21.1 and 25.8 months and for median OS were 22.4 and 32.0 months, showing that sunitinib then everolimus was superior across all measures.

Second-line therapy in mRCC

Multiple agents have been approved for second-line therapy in mRCC based on the results of several phase III studies (Table 2). Treatment options include sorafenib, axitinib, everolimus and, more recently, nivolumab. Table 2 outlines the current European Society of Medical Oncology (ESMO) guidelines, which will soon be changed to incorporate nivolumab, for which there is data with the highest level of evidence.

Sorafenib is a multikinase inhibitor of multiple growth factor receptors such as VEGFR, PDGFr, Flt-3 and c-Kit and Raf-1 (a member of RAF/MEK/ERK signaling pathway). Axitinib is a next-generation TKI, potent and highly selective for VEGF receptors 1, 2 and 3, and everolimus is an mTOR inhibitor.

In the phase III AXIS trial, axitinib was compared with sorafenib as second-line treatment in patients with advanced clear cell RCC who had received first-line treatment with sunitinib (54%), cytokines (35%), bevacizumab (8%) or temsirolimus (3%) [20]. Median PFS was 6.7 months with axitinib and 4.7 months with sorafenib (HR 0.665, 95%CI 0.544-0.812; p<0.0001). The most common adverse events were diarrhea, hypertension, and fatigue in axitinib recipients, and diarrhea, hand-foot syndrome and alopecia in the sorafenib group. These results led to the approval of axitinib for second-line therapy of advanced RCC.

The RECORD-1 trial provides data on the use of mTOR inhibitors after VEGFR inhibition-based therapy. In this phase III trial, patients who had received one or two previous treatments were randomized to everolimus or placebo. The results need to be interpreted with caution because only 21% of patients enrolled were receiving pure second-line therapy, progressing after first-line treatment with sunitinib. In this subgroup, patients treated with everolimus had a median PFS of 4.6 *versus* 1.8 months with placebo; 53% of patients received one TKI and cytokine (PFS 5.2 *vs* 1.8 months) and 26% were receiving third-line therapy after two TKIs (PFS 4.0 *vs* 1.8 months) [21, 22].

Nivolumab (BMS-936558) is a fully human, immunoglobulin (Ig) G4 monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor. The major role of PD-1 is to reduce the activity of T cells in peripheral tissues in case of an inflammatory response to infection, and to limit autoimmunity. This translates into a major immune resistance mechanism within the tumor microenvironment. PD-1 has two ligands (PD-1 ligand 1 [PD-L1] and PD-1 ligand 2 [PD-L2]); nivolumab binds to PD-1, preventing its interaction with PD-L1 and PD-L2, disrupting negative signaling to restore T-cell antitumor function [23]. The CheckMate 025 trial was designed to demonstrate OS superiority for nivolumab compared with everolimus in patients with mRCC previously treated with at least one prior TKI (including sunitinib or pazopanib) [24]. Nivolumab improved OS *versus* everolimus (25.0 *vs* 19.6 months, HR 0.75; p=0.002); the response to nivolumab was independent of PD-L1 expression. These findings resulted in the recent approval of nivolumab by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Table 2. Treatment options for second-line therapy of renal cell carcinoma (evidence levels according to ESMO Clinical Practice Guidelines 2014).

Prior treatment	Standard treatments	Optional treatments
Tyrosine kinase inhibitors	Axitinib (I, B) Everolimus (II, A)	Sorafenib (II, A)
Citokines	Axitinib (I, A) Sorafenib (I, A) Pazopanib (II, A)	Sunitinib (III, A)

There is controversy about the optimal sequence when choosing second-line therapy. For example, in patients who develop VEGFR TKI-resistance, is it better to continue treatment with a different agent with the same mechanism of action or to overcome cross-resistance by switching to an agent with a different mechanism of action? [25-29]. The only trial that has provided a direct comparison between second-line agents with different mechanisms of action is the INTORSECT phase III trial [30]. In this study patients with mRCC who had progressed on first-line sunitinib were randomized to receive temsirolimus or sorafenib. There was no significant difference in PFS between the two treatment groups (4.28 *vs* 3.91 months; p=0.19), while median OS was in favor of sorafenib (16.4 *vs* 12.3 months; p=0.014) [30]. These results could be interpreted to suggest an advantage for the VEGFR TKI-VEGFR TKI sequence compared with the VEGFR-TKI-mTOR inhibitor (mTORi) sequence, but it does not clarify the controversy because it compares two treatments that are not the best option in the second-line setting.

There is no direct comparison between axitinib and everolimus as second-line therapy in mRCC, but data from the two phase III trials (AXIS and RECORD-1) can be used to make an indirect comparison, although the main difference is that in the AXIS trial, axitinib is compared to sorafenib while in the RECORD-1 trial the comparator is placebo. Median PFS with axitinib and everolimus in patients with mRCC progression after first-line with sunitinib was quite similar (4.8 months with axitinib *vs* 4.6 months with everolimus). In the AXIS trial, one-third of patients had only received prior cytokines and were therefore effectively anti-VEGFR naïve. Conversely, in the RECORD-1 trial, only 21% of patients enrolled were receiving pure second-line therapy, and the remaining patients had received additional therapies prior to everolimus.

Finally, in the phase III SWITCH-I trial, patients were randomized to sorafenib followed by sunitinib, or vice versa, on progression or intolerable toxicity [31]. Total PFS was similar in the two treatment arms, demonstrating that clinical benefit was not significantly different based on the order of treatment.

Taken together, and in addition to retrospective analyses, the above data do not provide conclusive evidence for one sequence of treatment over another in second-line therapy for mRCC. It is possible that the availability of new data in this area could make the choice between a TKI and an mTOR inhibitor as second-line therapy irrelevant because new standards will soon be introduced in this setting.

Beyond second-line therapy

Most data relating to third-line treatments and beyond are derived from retrospective studies and subgroup analyses. In a retrospective study of 2,065 patients with mRCC treated in 23 centers in Italy, the sequence VEGF inhibitor (VEGFi)–VEGFi–mTORi was associated with improved survival compared with VEGFi–mTORi–VEGFi, particularly in patients with good prognostic risk at diagnosis of metastatic disease, and primary resistance to first-line therapy was a negative predictive and prognostic factor [32]. Subgroup analysis performed within the RECORD-1 trial assessed everolimus as a third-line drug, showing significant PFS benefit *versus* placebo (4.0 *vs* 1.8 months, HR 0.32; p<0.01), favoring the TKI-TKI-mTORi sequence [33].

The GOLD trial evaluated a third-line treatment in patients treated with one previous VEGFi-TKI and one previous mTORi: patients received dovitinib (an oral TKI of VEGFR and FGFr) or sorafenib. This trial showed no statistically significant differences between the two agents in terms of PFS (3.6 *vs* 3.7 months, respectively, HR 0.86, 95%CI 0.72-1.04; p=0.063) or interim OS (11.0 *vs* 11.1 months, respectively, HR 0.96, 95%CI 0.75-1.22) [34]. This study showed the efficacy of current agents for third-line therapy in mRCC. In addition, rechallenge with sunitinib in patients who progressed on prior sunitinib and another TKI or mTORi could be an option [35].

Future perspectives in mRCC

Recently, a randomized phase III trial compared the activity of cabozantinib with that of everolimus in relapsed mRCC. Cabozantinib is an oral, small-molecule TKI that targets VEGFR as well as MET and AXL. The METEOR study was designed to evaluate the superiority of cabozantinib over everolimus in terms of PFS in patients with pre-treated mRCC; secondary endpoints were OS and response rate (RR) [36]. In this trial, median PFS in patients treated with cabozantinib was 7.4 months compared with 3.8 months in those treated with everolimus (p<0.001); there was a 42% reduction in disease progression or relapse with cabozantinib *versus* everolimus. A subgroup analysis confirmed the PFS benefit irrespective of MSKCC group and number of previous antiangiogenic therapies. The ORR was 21% and 5% in the cabozantinib and everolimus arms, respectively, (p<0.001). A more recent report also showed a survival benefit: median OS was 21.4 months with cabozantinib and 16.5 months with everolimus (HR 0.66, 95%CI 0.53-0.83; p=0.00026) [37].

These results certainly improve the range of agents avail-

able, but the important question of the optimal sequence remains unanswered and in fact becomes more complicated. A sequential strategy including cabozantinib after nivolumab may be suitable for some patients previously treated with sunitinib or pazopanib. Moreover, a second TKI, such as axitinib or cabozantinib, could be an optional treatment to defer nivolumab to third-line therapy. The duration of response to a previous TKI, the aggressive behavior of the disease and the different toxicity profile of the available agents may be considered important factors in defining a sequential treatment strategy [38]. Unfortunately, molecular markers as predictors of response or resistance have not yet reached prime time.

Discussion and Conclusions

Nowadays, physicians have many effective options to treat mRCC. In the last decade, the introduction of new agents for this disease has improved survival and other clinical outcomes. Increasing recognition of the central role of the VEGF/VEGFR-pathway in the pathogenesis and development of RCC has provided and good rationale for inhibition of this pathway due to the frequent mutation of the VHL tumor suppressor gene in both clear cell RCC and in sporadic forms. This molecular signature renders RCC particularly dependent on angiogenesis and thus susceptible to angiogenesis inhibition with targeted agents.

In this review we have presented details of clinical trials of targeted therapy in RCC and tried to define an optimal treatment sequence. For second-line treatment after failure of therapy with VEGFR-TKIs, continued inhibition of the VEGF/VEGR pathway or switching to an mTOR inhibitor is recommended. These two options have some different targets and completely different toxicity profiles, but comparable efficacy. However, new data from two randomized, controlled, phase III trials in which cabozantinib and nivolumab showed an OS benefit compared with everolimus will change options for second-line therapy in mRCC. When these agents become widely available, the current standards, axitinib and everolimus are expected to shift to become part of, and improve, the choice of potential agents for third-line therapy. Criteria for choosing a treatment when more than one valid option exists remain to be defined, but continuous development of active and effective agents is very likely to lead to further improvements in prognosis for patients with mRCC.

Lack of direct comparative data on newer agents makes the choice difficult. However, in the current treatment paradigm it is unlikely that the "one sequence fits all" scenario is realistic. The sequence in which the available targeted agents are given needs to be carefully planned and individualized for each patient to optimize therapy and achieve the best outcomes. Factors to take into account include the safety profile of drugs, comorbidities of patients and tumor biology. Better knowledge of the mechanisms underlying renal cancer tumorigenesis could provide complementary information, identify predictors of response to drugs [39], and help the physician to make the best choice for their patient.

Acknowledgments

The authors thank Nicola Ryan, an independent medical writer, who provided native English editing and journal styling on behalf of HPS. This editorial assistance was funded by PharmaMar, Spain.

Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

References

1. American Cancer Society: Cancer Facts and Figures 2016. Available from http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2016/. Last accessed: March 9 2016.
2. Cho E, Adami HO, Lindblad P. Epidemiology of renal cell cancer. Hematol Oncol Clin North Am 2011;25(4):651-5.
3. Escudier B, Porta C, Schmidinger M et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii49-56.
4. Iacovelli R, Sternberg CN, Porta C et al. Inhibition of the VEGF/VEGFR pathway improves survival in advanced kidney cancer: a systematic review and meta-analysis. Curr Drug Targets 2015;16(2):164-70.
5. Rini BI. New strategies in kidney cancer: therapeutic advances through understanding the molecular basis of response and resistance. Clin Cancer Res 2010;16(5): 1348-54.
6. Chen Y, Sun Y, Rao Q et al. Androgen receptor (AR) suppresses miRNA-145 to promote renal cell carcinoma (RCC) progression independent of VHL status. Oncotarget 2015;6:31203-15.
7. Ghosh AP, Marshall CB, Coric T et al. Point mutations of the mTOR-RHEB pathway in renal cell carcinoma. Oncotarget 2015;6:17895-910.
8. Liu Q, Jin J, Ying J et al. Epigenetic inactivation of the candidate tumor suppressor gene ASC/TMS1 in human renal cell carcinoma and its role as a potential therapeutic target. Oncotarget 2015;6:22706-23.
9. D'Aniello C, Cavaliere C, Pisconti S et al. Long-term re-

sponse to pazopanib in an elderly man with mRCC. A case report. Tumori 2014;100(6):e305-8.
10. Johannsen M, Staehler M, Ohlmann CH et al. Outcome of treatment discontinuation in patients with metastatic renal cell carcinoma and no evidence of disease following targeted therapy with or without metastasectomy. Ann Oncol 2011;22(3):657-63.
11. Albiges L, Oudard S, Negrier S et al. Complete remission with tyrosine kinase inhibitors in renal cell carcinoma. J Clin Oncol 2012;30(5):482-7.
12. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356(22):2271-81.
13. Escudier B, Pluzanska A, Koralewski P et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370(9605):2103-11.
14. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356(2):115-24.
15. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28(6):1061-8.
16. Sternberg CN, Hawkins RE, Wagstaff J et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013;49(6):1287-96.
17. Motzer RJ, Hutson TE, Cella D et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369(8):722-31.
18. Escudier B, Porta C, Bono P et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol 2014;32(14):1412-8.
19. Motzer RJ, Barrios CH, Kim TM et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32(25):2765-72.
20. 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(9807):1931-9.
21. 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(9637):449-56.
22. Motzer RJ, Escudier B, Oudard S et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 2010;116(18):4256-65.
23. Wang C, Thudium KB, Han M et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res 2014;2(9):846-56.
24. Motzer R, Escudier B, McDermott D et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015:373(19):1803-13.
25. Sonpavde G, Choueiri TK, Escudier B et al. Sequencing of agents for metastatic renal cell carcinoma: can we customize therapy? Eur Urol 2012;61(2):307-16.
26. Escudier B, Gore M. Sequencing therapy in metastatic renal cell cancer. Semin Oncol 2013;40(4):465-71.
27. Schmidinger M. Improving outcomes in metastatic clear cell renal cell carcinoma by sequencing therapy. Am Soc Clin Oncol Educ Book 2014:e228-38.
28. Calvo E, Ravaud A, Bellmunt J. What is the optimal therapy for patients with metastatic renal cell carcinoma who progress on an initial VEGFr-TKI? Cancer Treat Rev 2013;39(4):366-74.
29. Calvo E, Grünwald V, Bellmunt J. Controversies in renal cell carcinoma: treatment choice after progression on vascular endothelial growth factor-targeted therapy. Eur J Cancer 2014;50(7):1321-9.
30. Hutson TE, Escudier B, Esteban E et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32(8):760-7.
31. Eichelberg C, Vervenne WL, De Santis M et al. SWITCH: A randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer. Eur Urol 2015;68(5):837-47.
32. Iacovelli R, Cartenì G, Sternberg CN et al. Clinical outcomes in patients receiving three lines of targeted therapy for metastatic renal cell carcinoma: results from a large patient cohort. Eur J Cancer 2013;49(9):2134-42.
33. Calvo E, Escudier B, Motzer RJ et al. Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. Eur J Cancer 2012;48(3):333-9.
34. Motzer RJ, Porta C, Vogelzang NJ et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. Lancet Oncol 2014;15(3):286-96.
35. Zama IN, Hutson TE, Elson P et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer 2010;116(23):5400-6.
36. Choueiri TK, Escudier B, Powles T et al. METEOR Investigators. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373(19):1814-23.
37. Choueiri TK, Escudier B, Powles T et al. METEOR Investigators. Cabozantinib versus everolimus in advanced renal-cell carcinoma (METEOR): final results from a randomized, open-label, phase 3 trial. Lancet Oncol 2016;17(7):917-27.
38. Procopio G, Ratta R, Grassi P. Evolving treatment landscape in metastatic renal cell carcinoma: where are we now? Expert Rev Anticancer Ther 2016;16(2):133-5.
39. D'Aniello C, Cavaliere C, Licchetta A et al. Metastatic renal cancer: prognostic and predictive biomarkers review. WCRJ 2014;1(3):e289.