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Abstract:
Targeted therapies have introduced a paradigm shift in the management of metastatic renal cell carcinoma. Currently, four molecules (sunitinib, pazopanib, bevacizumab plus interferon, temsirolimus) are considered in first-line therapy, and three other molecules for second, or subsequent lines of therapy (everolimus, axitinib, sorafenib). In addition, other molecules and sequencing schemes are being tested in ongoing phase II/III studies. We conducted a systematic review using PubMed and several other databases up to December 2011 of prospective and retrospective studies on treatment management of metastatic renal cell carcinoma using targeted therapies, with a special focus on use of sequential treatment. Based on phase III data, the optimal sequencing scheme for patients with clear cell or even non-clear cell histological subtype appears to consist of sunitinib, followed by axitinib, followed by everolimus. Subsequent treatment options rely on lower evidence studies and could consist of fourth-line sorafenib or sunitinib rechallenge. Such therapies would qualify as last recourse options. In another context, temsirolimus may be used in patients who fulfill the Memorial Sloan-Kettering Cancer Center poor risk criteria or who have poor performance status. We conclude that in the current setting, sequential therapy represents the cornerstone of effective management of metastatic renal cell carcinoma.

Keywords: metastatic renal cell carcinoma, sequential therapy, targeted therapies

Introduction

Historically, the median survival of patients with metastatic renal cell carcinoma (MRCC) was 10 months [Motzer *et al.* 1999]. The introduction of targeted therapies resulted in a paradigm shift in the management of this malignancy. The use of first-line agents resulted in a doubling of overall survival (OS) [Escudier *et al.* 2010; Motzer *et al.* 2009]. Sequential therapy schemes proposed by Escudier and colleagues, which rely on consecutive use of several different agents, have the ability to increase the duration of progression-free survival (PFS) well beyond 2 years, and that of OS even further [Escudier *et al.* 2009b]. Based on phase III studies confirming the efficacy of targeted therapies in first, second, and subsequent lines, sequential therapy represents the cornerstone of effective management of MRCC.

The publication of sunitinib [Motzer *et al.* 2007], bevacizumab plus interferon [Escudier *et al.* 2007b], and sorafenib [Escudier *et al.* 2007a] efficacy and tolerability data in 2007 provided pivotal first- and second-line data supporting the benefits of novel targeted therapies for the management of MRCC. Since then, numerous novel agents have been introduced. All of those have been supported by statistically significant benefits in well designed randomized, controlled trials. Currently, phase III data are available for four first-line [Escudier *et al.* 2007b, 2010; Hudes *et al.* 2007; Motzer *et al.* 2007, 2009; Rini *et al.* Rini *et al.* 2008a, 2010; Sternberg *et al.* 2010], and three subsequent-line agents [Escudier *et al.* 2007a, 2009a; Motzer *et al.* 2008, 2010; Rini *et al.* 2011]. Additional studies are available to substantiate the use of these molecules in various

lines of therapy [Escudier *et al.* 2009c; Mackenzie *et al.* 2011; Motzer *et al.* 2006; Reeves *et al.* 2011; Zama *et al.* 2011] However, it may be difficult to disentangle the rationale supporting the use of one first-line agent relative to another. It may be even more challenging to identify such rationale for subsequent lines of therapy. In this review, we outline an evidence-based approach to the sequential selection of various agents.

First-line therapy

Clear cell histology metastatic renal cell carcinoma

Patients with clear cell histology MRCC may benefit from three first-line molecules, namely sunitinib, bevacizumab plus interferon, and pazopanib. All three have proven efficacy in randomized, controlled phase III trials [Escudier *et al.* 2007b, 2010; Motzer *et al.* 2007, 2009; Rini *et al.* 2008a, 2010; Sternberg *et al.* 2010].

Sunitinib. Sunitinib, a tyrosine kinase inhibitor (TKI), showed median PFS of 11 months *versus* 5 months for interferon as first-line treatment in 750 patients with MRCC [Motzer *et al.* 2007, 2009]. These data were corroborated by findings from 4564 patients treated with sunitinib in an expanded access trial [Gore *et al.* 2009] These data were further corroborated by several observational first-line studies [Barrios *et al.* 2012; Castellano *et al.* 2009; Heng *et al.* 2009; Motzer *et al.* 2007]. Therefore, sunitinib first-line data (combined $n = 1373$) represent the most generalizable among all available first-line molecules.

Bevacizumab plus interferon. The use of bevacizumab plus interferon, a vascular endothelial growth factor antibody, is supported by two large-scale phase III studies. One study focused on European patients ($n = 649$) [Escudier *et al.* 2007b, 2010] and the second on North American patients ($n = 732$) [Rini *et al.* 2008a, 2010]. The duration of bevacizumab plus interferon treatment efficacy ranges from 8 to 10 months. After that period, most patients will require second-line therapy.

Pazopanib. Pazopanib, a TKI, showed efficacy as first-line treatment in 232 patients with clear or predominantly clear cell locally advanced or metastatic renal cell carcinoma. In that trial, a durable PFS (median 8 months) and favorable toxicity profile were recorded. When pazopanib was indirectly compared with sunitinib, median PFS duration was comparable (8 *versus* 11 months), and pazopanib patients were less likely to experience an adverse event during treatment. For example, the rates of grade 3 or 4 fatigue (2% *versus* 7%), hypertension (4% *versus* 8%), hand-food syndrome (HFS) (<1% *versus* 5%), neutropenia (4% *versus* 12%) were all in favor of pazopanib.

Dilemma in choosing the molecule of choice for first-line status

Given the availability of the aforementioned molecules that have distinctively established themselves in the first-line context within separate phase III designs, there is a dilemma in selecting the most optimal first-line molecule. Most would agree that sunitinib represents the ideal first-line standard of care option. In addition to the abundance of studies that have reported on the efficacy of sunitinib, other advantages, such as availability of data substantiating the efficacy of second (axitinib) and subsequent (everolimus) lines of therapy after sunitinib failure, represent additional important considerations if first-line sequential therapy with the largest evidence base is sought [Motzer *et al.* 2008, 2010; Rini *et al.* 2011].

However, others may contest that bevacizumab with interferon or pazopanib might represent an equally viable first-line standard of care option. With respect to bevacizumab in combination with interferon, unfortunately there are limited data to support the sequential use of other targeted agents after bevacizumab plus interferon failure. Existing phase III reports examining everolimus and axitinib included 24 (9%) and 29 (8%) patients who failed to respond to bevacizumab respectively [Motzer *et al.* 2008; Rini *et al.* 2011]. In the axitinib trial, patients who were previously treated with bevacizumab plus interferon had a lower PFS when given axitinib than patients who received sorafenib (4.2 *versus* 4.7 months, respectively, $p = 0.1$).

Sequential treatment with targeted therapies after bevacizumab plus interferon failure is supported by lower evidence level data that hint at a modest efficacy of sunitinib, pazopanib, or sorafenib as second-line options, following bevacizumab plus interferon failure [Bracarda *et al.* 2011; Garcia *et al.* 2010; Hutson *et al.* 2010; Rini *et al.* 2008b]. However, the statistical significance of these data is lacking. In consequence, efficacy may be limited and remains unproven, and thus, reimbursement

of sequential agents after bevacizumab plus interferon failure may represent an important obstacle.

With respect to pazopanib, better tolerability and comparable efficacy, relative to the standard of care sunitinib, may represent important considerations for the selection of pazopanib as a first-line agent of choice. However, the weight of evidence supporting the use of pazopanib first-line is modest relative to sunitinib. First, apart from the phase III trial, no other study examined pazopanib as first-line treatment. Conversely, first-line sunitinib data originate from multiple studies (combined n = 1373) [Barrios *et al.* 2012; Castellano *et al.* 2009; Heng *et al.* 2009; Motzer *et al.* 2007]. Second, the phase III data sample size for pazopanib was substantially less than for sunitinib (n = 232 *versus* 750) [Motzer *et al.* 2007; Sternberg *et al.* 2010]. Many patients in the pazopanib trial consisted of cytokine-refractory individuals (n = 202, 46%). Finally, the limitation of pazopanib use first line is particularly undermined by the lack of published data that specifically validate or quantify the efficacy of sequential therapies after pazopanib failure. Indeed, no phase III studies focusing on second- or third-line therapies included pazopanib-refractory patients. The efficacy of data for sequential use of targeted therapies after pazopanib failure is nonexistent. In consequence, unfavorable reimbursement considerations for second-line therapy after pazopanib failure may represent an additional important argument against first-line pazopanib use.

On that note, an ongoing phase III noninferiority trial COMPARZ will test the efficacy and tolerability of first-line pazopanib *versus* sunitinib [ClinicalTrials.gov identifier: NCT00720941]. In addition, patient preference will be examined in a randomized, sequential trial of 160 patients on pazopanib or sunitinib followed by patient-based choice of either agent [ClinicalTrials.gov identifier: NCT01064310]. These data will provide a direct comparison and will avoid the biases related to indirect trial comparisons. Such indirect comparisons may be more invalid in some comparisons than in others. The first-line pazopanib patient population represents a relatively special patient group since patients were recruited from very select locations where first-line therapy was unavailable. Based on ethical considerations, a first-line placebo-controlled study would not have been feasible in North America or Europe in the same time period. This results in complete absence of North American or European patients within the cytokine-naïve patient subgroup (true first-line patients). In consequence, the patient and MRCC phenotype of cytokine-naïve pazopanib patients may differ from those from Western Europe or North America.

If pazopanib were to show superiority relative to sunitinib, it is questionable whether such a result would affect clinical practice. This skepticism is based on the lack of evidence-based sequencing options after first-line pazopanib failure.

Other molecules competing for first-line status

Although not formally tested in the first-line context, at least two other molecules (everolimus and sorafenib) may also challenge sunitinib as the first-line standard of care in patients with MRCC.

Everolimus versus *sunitinib*

Sunitinib's status as first-line agent is also challenged by everolimus. The ongoing RECORD-3 (Renal Cell Cancer Treatment with Oral RAD001 Given Daily) noninferiority phase III trial will provide efficacy and tolerability data for sunitinib followed by everolimus *versus* everolimus followed by sunitinib sequencing schemes (n = 390) [Knox *et al.* 2010]. The combined PFS of these sequences will shed light on the best order of administration of these two molecules. Toxicity data will complement efficacy findings.

Even though noninferiority of the everolimus/sunitinib sequence *versus* sunitinib/everolimus represents the trial's primary hypothesis, three potential outcomes of this trial are possible: clear superiority of initial sunitinib; equivalence of both regimens; or clear superiority of initial everolimus. If the first scenario prevails, sunitinib will remain the initial standard of care. In the case of the third scenario, the use of everolimus first line followed by sunitinib second line will become a valid option relative to first-line sunitinib. However, the use of first-line everolimus followed by sunitinib will result in a dilemma about sequencing of third-line treatment. The dilemma may be explained as follows: to date, no phase III trial has tested the efficacy and tolerability of any molecule after failure of first-line everolimus and second-line sunitinib. An ongoing third-line trial will compare the efficacy of two third-line therapies (dovitinib *versus* sorafenib) after failure of a first-line TKI and a second-line mammalian

target of rapamycin (mTOR) [ClinicalTrials.gov identifier: NCT01223027]. However, it will not provide any direct evidence regarding third-line therapy after failure of a first-line mTOR and a second-line TKI. Therefore, under the third scenario, new trials will be required to provide evidence-based criteria for the selection of third-line agents. In that context, existing data that originated from either the phase III axitinib trial (sunitinib or cytokine refractory followed by second-line axitinib) or the everolimus trial will no longer be applicable.

If both regimens show equivalence (the second scenario), it is likely that sunitinib will remain the first-line standard of care. An alternative approach (use of another agent second line) would result in the same dilemma as outlined in the description of the third scenario.

Sorafenib versus *sunitinib.* An ongoing phase III study will provide efficacy and toxicity regarding the sequencing of sunitinib followed by sorafenib *versus* sorafenib followed by sunitinib [ClinicalTrials.gov identifier: NCT00732914]. Again three outcomes are possible. These closely resemble the RECORD-3 scenarios described above. An equivalence between the two sequences or superiority of upfront sorafenib followed by second-line sunitinib would result in the same management dilemma, as outlined for the scenario that stipulated superior outcomes with first-line everolimus followed by second-line sorafenib. In consequence, such findings may not be universally adopted.

Other limitations of head-to-head first-line studies

Lack of acceptance of data from head-to-head trials may also stem from other characteristics of such trials. For example, the sample size of head-to-head trials may undermine their generalizability relative to existing phase III first-line sunitinib data. An estimated 390 patients will be enrolled in the RECORD-3 study within participating centers in North America, Europe, and Asia. Conversely, the sequential trial of sunitinib/sorafenib or sorafenib/sunitinib will enroll an estimated 346 patients, who exclusively originate from Germany. These numbers do not favorably compare with 750 patients enrolled in the pivotal phase III sunitinib trial [Motzer *et al.* 2007]. In addition, restricted recruitment in one Western European country may undermine the generalizability of their findings to other geographic regions, where patients and disease characteristics may be different. These considerations further undermine the potential acceptance of the final results from a sequential trial, or even the RECORD-3 and COMPARZ findings.

Taken together, four molecules are available for first-line use in patients with MRCC. Sunitinib currently represents the standard of care. The existing studies, such as those on axitinib and everolimus, provide level 1 evidence regarding second-line and second/third-line sequencing for sunitinib respectively. Use of alternative first-line therapies, despite their proven efficacy in phase III trials, such as bevacizumab plus interferon or pazopanib, does not necessarily allow the direct use of these data. This consideration renders the clinical applicability of those molecules problematic. Use of novel agents that are being tested in head-to-head phase III (sequential therapy sunitinib/sorafenib *versus* sorafenib/sunitinib) or phase II (RECORD-3) studies may result in data that will require a major paradigm shift, but will lack weight due to sample size considerations or patient selection. Based on these considerations, it is unlikely that novel data from ongoing studies will displace sunitinib from its established first-line status. However, methodological modifications of the RECORD-3 study (larger sample size and conversion from phase II to phase III status) could result in more valid and acceptable findings.

Poor risk and non-clear cell histology metastatic renal cell carcinoma

Temsirolimus, a mTOR inhibitor, represents the first molecule that demonstrated an OS benefit relative to the standard of care, interferon [Hudes *et al.* 2007]. The temsirolimus study focused on patients with poor risk criteria according to the Memorial Sloan-Kettering Cancer Center (MSKCC) definition [Motzer *et al.* 1999, 2002, 2004]. This consideration restricts evidence-based use of temsirolimus to a very narrow subset of individuals with strict poor risk MRCC criteria. Motzer and colleagues estimated the contemporary proportion of patients with initial poor risk status at 5% when a tertiary care referral population was examined [Patil *et al.* 2010]. At less specialized institutions, this proportion will be situated well below this figure. In consequence, very few patients qualify for first-line temsirolimus based on the MSKCC criteria alone.

The presence of non-clear cell histological subtype represents another consideration for first-line use of temsirolimus. At initial MRCC diagnosis, approximately 20% of patients harbor non-clear cell histology [Hudes *et al.* 2007] and may qualify for temsirolimus. Of those, only 5% may be considered as poor risk, which means that only 1% of newly diagnosed individuals with MRCC may qualify for temsirolimus based on evidence-based criteria.

An additional issue is that the use of first-line temsirolimus poses a problem once this therapy fails, as limited data exist regarding the efficacy of other targeted agents after temsirolimus failure. Interestingly, temsirolimus-refractory patients subsequently treated with axitinib demonstrated a PFS of 10.1 months relative to sorafenib in one phase III trial. However, that observation failed to reach statistical significance, which is possibly related to the low number of patients who were included in this subset (n = 12, 3%) [Rini *et al.* 2011]. Based on this consideration, an evidence-based rationale for use of subsequent lines in the case of temsirolimus failure may represent a challenge.

Sunitinib represents an alternative to temsirolimus in patients with poor risk features. Sunitinib phase III, first-line data include a subset of individuals with poor risk features (n = 23, 6%) [Motzer *et al.* 2007]. In consequence, treatment with first-line sunitinib in patients with poor risk features is in accordance with level 1 evidence. Moreover, access to subsequent lines of therapy may represent a lesser challenge when sunitinib is used instead of first-line temsirolimus. That said, temsirolimus remains the agent of choice in patients with poor risk features whose performance status or life expectancy render second and subsequent lines of therapy unlikely.

Alternatives also include sorafenib. The use of this agent is supported by lower evidence level data consisting of a small-scale, uncontrolled case series (n = 53) [Choueiri *et al.* 2008]. In that report, the efficacy of sunitinib (PFS 11.9 months), as well as other agents such as sorafenib (PFS 5.1 months), in individuals with non-clear cell histology has been observed. Nonetheless, temsirolimus maintains its position as the molecule of choice in patients with non-clear cell MRCC. However, in the context that no evidence-based data exist to support the use of second-line agents following temsirolimus failure, approval of sequential therapies in patients with temsirolimus-refractory disease may represent a challenge.

Second- and third-line therapy

Two phase III trials have confirmed the efficacy and tolerability of two sequential therapy molecules: everolimus and axitinib [Motzer *et al.* 2008, 2010; Rini *et al.* 2011]. The pivotal everolimus trial data (n = 410) confirmed the validity of sequential therapy based on superior PFS in the active treatment arm relative to placebo and best supportive care (4.9 *versus* 1.9 months). Within this study, most patients received multiple agents prior to randomization between everolimus and best supportive care, whereas less than 5% of patients received first-line sunitinib or sorafenib only, prior to randomization [Motzer *et al.* 2008]. Moreover, of all the patients on everolimus, 26% received two TKIs (sorafenib and sunitinib). Based on these facts, evidence from the everolimus trial can be considered to support the molecule's use in second- and subsequent-line therapy. This is particularly important in the context of the recently released findings from the axitinib phase III trial data.

The axitinib trial demonstrated superior efficacy of axitinib relative to sorafenib (6.7 *versus* 4.7 months) in patients previously given either sunitinib alone (4.8 *versus* 3.4 months) or cytokine alone (12.1 *versus* 6.1 months) [Rini *et al.* 2011]. Data from the axitinib trial (n = 723) show important differences relative to the everolimus trial. Specifically, the axitinib population represents a true second-line population. Conversely, the majority of patients (~95%) received everolimus as third-line treatment [Motzer *et al.* 2008]. Moreover, in more than half of the patients taking axitinib their condition had failed to respond to sunitinib alone (n = 369, 54%). In addition, the sample size of the axitinib trial (n = 723) is substantially larger than that of the everolimus trial (n = 410). It is of interest that the sunitinib-only subgroup of the axitinib trial is similar in size relative to the entire everolimus study (n = 369 *versus* 410).

Based on these considerations, it may be argued that the axitinib phase III data are better suited to support second-line therapy. Conversely, the everolimus phase III data appear better suited to support third or subsequent lines of therapy. Under this premise, axitinib may be interpreted as the standard of care in second-line therapy. After failure of two consecutive lines of therapy, the everolimus

phase III study data may be used to support the administration of everolimus as third-line therapy.

An alternative interpretation of these data would consider the everolimus phase III report as pivotal second-line findings. Under such a premise, there would be no space for axitinib use since, to date, no phase III data have confirmed a statistically significant efficacy of axitinib after failure of second-line mTOR therapy.

Taken together, the existing second-line data indicate that axitinib should be considered as second-line standard of care. This treatment should be followed by sequential everolimus as standard third-line therapy. This sequence allows the maximal use of phase III data to select first-, second- and third-line therapy.

Alternative second-line regimens

Based on the availability of two molecules supported by phase III data, it does not appear warranted to rely on agents other than axitinib or everolimus in second-line therapy. An exception may be patients whose condition failed to respond to standard of care and who qualify as poor risk, including those with a poor performance status. Such individuals may benefit from temsirolimus based on its favorable toxicity profile. Of molecules tested as second-line therapy after sunitinib failure, sorafenib data offer the most generalizable findings [Buchler *et al.* 2012; Di Lorenzo *et al.* 2009; Dudek *et al.* 2009; Sablin *et al.* 2010]. However, no evidence level 1 findings exist.

Alternative third-line regimens

Efficacy of everolimus militates against alternative agents. As in the alternative second-line therapy outlined above, patients with poor risk and poor performance status may benefit from temsirolimus. For third-line therapy, sorafenib data remain the most robust when lower evidence level studies are considered [Di Lorenzo *et al.* 2010].

Ongoing third line trials

TKI258 (dovitinib *versus* sorafenib) is an ongoing phase III trial in patients with MRCC [ClinicalTrials.gov identifier: NCT01223027]. The trial will enroll an estimated 550 randomized patients whose condition has failed to respond to first-line sunitinib and second-line everolimus. A possible outcome may be better efficacy and tolerability of dovitinib. Under such a premise, dovitinib would be considered for the standard of care after failure of everolimus. Since everolimus use will likely focus on patients receiving third-line therapy (after failure of sunitinib and axitinib), dovitinib will likely become the standard of care in fourth-line therapy. An alternative outcome would result in the superiority of sorafenib. Under this premise, sorafenib may become the fourth-line standard of care.

Fourth-line therapy

Currently, no phase III data support the efficacy of fourth-line therapy, with the exception of everolimus after failure of three treatment lines [Motzer *et al.* 2008, 2010]. Other alternatives are not evidence based. Instead, such treatments represent last recourse options for patients whose performance status and other considerations support the potential for treatment benefits and confirm the ability to tolerate such measures. Options include sorafenib, based on the efficacy of this molecule after failure of first-line sunitinib and a second-line mTOR inhibitor [Di Lorenzo *et al.* 2010]. Alternatively, temsirolimus may still be considered in patients with poor risk characteristics. Case series suggest the potential efficacy of sunitinib rechallenge, especially following a sunitinib exposure-free interval of more than 6 months [Zama *et al.* 2011]. Finally, other molecules that have not been used may be considered as last recourse alternatives.

Conclusion

Several agents are available to treat patients with MRCC. Based on phase III data, the optimal sequencing scheme for patients with clear cell, or even non-clear cell, histological subtype appears to consist of sunitinib, followed by axitinib, followed by everolimus. Subsequent treatment options rely on lower evidence studies and could consist of fourth-line sorafenib or sunitinib rechallenge. Such therapies would qualify as last recourse options. In another context, temsirolimus may be used in patients who fulfill the MSKCC poor risk criteria and who have a poor performance status.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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