Axitinib in renal cell carcinoma: now what do we do?

Ian D. Davis

Monash University Eastern Health Clinical School, Level 2, Box Hill, Victoria 3128, Australia

Correspondence to: Ian D. Davis, MBBS (Hons), PhD, FRACP, FAChPM. Monash University Eastern Health Clinical School, Level 2, 5 Arnold St, Box Hill, Victoria 3128, Australia. Email: ian.davis@monash.edu.

Abstract: Axitinib is a potent small molecule tyrosine kinase inhibitor with relative specificity for vascular endothelial growth factor (VEGF) receptors. Initial studies indicated promising levels of activity and a favourable safety profile in advanced renal cell carcinoma (RCC) and the drug has now been approved for use in the second line setting in this disease. It was logical then to move axitinib into trials in the treatment-naïve population. The AGILE clinical trial compared axitinib to another drug, sorafenib, which has broader specificity for its kinase targets. The AGILE trial failed to meet its primary objective of improving progression-free survival (PFS). This editorial examines the trial in detail and speculates upon possible reasons for this failure and what the future might hold for axitinib and other therapies.

Keywords: Axitinib; renal cell carcinoma (RCC); sorafenib; clinical trials

Submitted May 30, 2014. Accepted for publication Jun 02, 2014.
doi: 10.3978/j.issn.2218-676X.2014.06.07
View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2014.06.07

Few areas of oncology have undergone changes as profound as those we have seen over the last few years in the field of renal cell carcinoma (RCC). Clinicians and our patients are now spoiled for choice, with high level evidence for a range of treatments showing benefit in the first line and second line treatment settings (1-8). Occasionally responses to some of these agents have been extraordinarily striking (9), and patients with advanced clear cell RCC can now expect a response or clinical benefit in around 75% of cases. Advanced RCC, once almost untreatable, has now become one of our most treatable cancers and a generation of clinicians is growing up without the same sense of despair that many of us experienced for so long.

However, our enthusiasm and optimism still require tempering as many questions and issues still remain. Some of the problems still facing us include the following:

(I) The best outcomes to date have been for clear cell RCC. Patients with non-clear cell RCC are still largely bereft of effective therapies;

(II) Some clinical indicators, such as development of hypertension on treatment, predict for therapeutic drug levels and correlate with efficacy. These assessments can only be made once treatment has commenced. No clinical or tissue biomarkers have yet been defined that allow clinicians to make rational choices regarding first line therapies prior to commencing treatment;

(III) Evidence to guide treatment choices in the second- and subsequent-line settings is still incomplete. Everolimus, temsirolimus, sorafenib and axitinib have been shown to be active in the post-first-line setting (4,7,10), however, the designs for those pivotal trials did not provide evidence to support decisions about which patients should continue with a vascular endothelial growth factor receptor (VEGFR) targeted therapy and which should switch to one targeting mammalian target of rapamycin (mTOR). A recent trial of dovitinib, which also targets fibroblast growth factor receptors, did not show it to be superior to sorafenib in the third-line setting (11);

(IV) Many of the available drugs have substantial "off-target" effects on kinases other than VEGFR family members (12). These effects may contribute to some of the toxicities of these drugs, but may also mediate clinical efficacy in some patients. Drugs with the narrowest spectrum of activity can have

fewer or more predictable side effects but have not yet demonstrated improved efficacy, although issues of trial design may have confounded interpretation of some trials. Bevacizumab is arguably the most specific drug targeting VEGF-A and has little activity as a single agent (13);

(V) Currently available drugs remain expensive and availability for patients varies around the world depending on local approval and reimbursement conditions.

The AGILE study by Hutson *et al.* (14) casts light on some of these questions but leaves many unanswered. Axitinib is a potent tyrosine kinase inhibitor with relative selectivity for VEGFR family members. Axitinib has already been shown to be active in the second-line setting AXIS trial (7), which compared axitinib to sorafenib in patients who had received first line treatment either with sunitinib, bevacizumab plus interferon-alpha, temsirolimus or cytokines. A statistically significant benefit was observed for the axitinib group, with a median progression-free survival (PFS) of 6.7 months with axitinib compared to 4.7 months for sorafenib [hazard ratio (HR) 0.665, 95% confidence intervals (CIs) 0.544-0.812, one-sided P<0.0001]. The AXIS trial allowed uptitration of axitinib dose in patients who did not experience hypertension and subsequent reports indicated that this brought serum drug levels in those patients into the therapeutic range (15). Axitinib dose titration in this clinical setting is now standard.

Subgroup analyses of the AXIS study showed that most of the benefit from axitinib was observed in patients who had not previously received VEGF-targeted therapy, i.e., in the patients who have previously received cytokines (median PFS 12.1 versus 6.5 months, HR 0.464, P<0.0001). A similar trend was observed for patients who had previously only received temsirolimus although small numbers meant that this was not statistically significant (median PFS 10.1 versus 5.3 months, HR 0.511, P=0.1425). In comparison, median PFS with axitinib treatment in those who had previously received sunitinib was 4.8 months compared to 3.4 months for sorafenib (HR 0.741, P=0.0107), a result that is statistically significant but of much smaller magnitude. PFS for axitinib in patients who had previously received bevacizumab was similar to those receiving sorafenib (4.2 months for axitinib versus 4.7 months for sorafenib, HR 1.147, P=0.6366).

The AXIS results therefore suggested that axitinib might be most effective in patients who had not previously received VEGFR-targeted therapy. The AGILE study by Hutson *et al.* was designed to address this question directly (14). The trial was an international phase 3, randomised, open label study comparing axitinib to sorafenib in treatment-naïve patients with metastatic RCC. Key eligibility criteria included at least a component of clear cell carcinoma; measurable disease by RECIST; good performance status; no prior therapy, except that prior cytokines were permitted if disease recurrence was at least 6 months after treatment; no uncontrolled hypertension. Participants were randomised 2:1 to receive axitinib or sorafenib after stratification by Eastern Cooperative Oncology Group (ECOG) performance status. Participants randomised to sorafenib received 400 mg twice daily and this dose was not allowed to be escalated; participants randomised to axitinib were commenced on a dose of 5 mg twice daily and the dose could be escalated in patients who did not experience adverse events of grade 2 or more. This dosing approach, shown to be effective in the AXIS trial, could have had the effect of biasing results in favour of axitinib.

The primary endpoint of the study was PFS. This is frequently used as a surrogate endpoint but response assessment to this class of drugs can be difficult, particularly if metastatic lesions become hypodense or cystic but increase in volume. Secondary endpoints included response rate and response duration, both also subject to interpretation; overall survival; safety; and patient-reported outcomes. The trial had 90% power to detect a median PFS of 9.8 months with axitinib against the null hypothesis of 5.5 months PFS for sorafenib, representing a HR of 0.56 with one-sided P=0.025 and requiring 247 patients. This difference of 4.3 months represents a 78% improvement over sorafenib, which in retrospect was probably very optimistic. Power calculations for trials using sorafenib as the comparator continue to use this figure of 5.5 months (2), although more recent studies have shown that PFS with sorafenib is probably considerably higher (16).

Eventually a total of 288 patients entered the AGILE study, with 192 receiving axitinib and 96 randomised to sorafenib; three patients randomised to axitinib were not treated. Baseline characteristics of both groups were well matched. A planned interim analysis occurred after 80 patients had died or experienced disease progression. The data monitoring committee subsequently increased the number of patients requiring progression to 169. The final reported analysis occurred after 171 patients had died or demonstrated disease progression; most patients had discontinued treatment by then due to these reasons.

The trial did not meet its primary endpoint. The median

PFS for patients receiving axitinib was 10.1 months (95% CI: 7.2-12.1) versus 6.5 months (4.7-8.3) for sorafenib [HR 0.77 (0.56-1.05), one-sided P=0.038 which is not statistically significant]. A prespecified subgroup analysis suggested that PFS was better in patients with ECOG performance status 0. No complete responses were seen although there were more responders with axitinib. Dose interruptions for toxicity were similar between the two groups and very few patients ceased treatment due to toxicity. The endpoint of overall survival remains immature although it would appear unlikely that a difference will now be observed. Patient-reported outcomes were similar between the two groups.

What went wrong? Previous studies suggested that axitinib might work best in this treatment-naïve setting. The authors have speculated on some possible factors to account for the negative results. One key difference between this study and the AXIS trial was that AXIS predominantly recruited from North America whereas AGILE had substantial recruitment from Eastern Europe. Three countries (Ukraine, Russia, India) accounted for 153 (53%) of the participants, and 25% of the study population was Asian. Could this have meant that patients entered the study later in their disease course or with a higher burden of disease? This point is not directly assessed in the paper. However, the trial was restricted to patients of good performance status and only nine patients in total had poor prognostic features. The median PFS of 6.5 months in the sorafenib arm is quite respectable compared to other previous trials. This suggests that the disease state at the time of study entry was not extreme and is unlikely to account for the smaller than expected difference between the groups.

Could it have been a dosing or pharmacokinetic phenomenon? The trial design allowing dose titration implied that therapy was more likely to be optimised in the axitinib group and this was supported by the observation that patients receiving axitinib also tended to receive treatment for longer, experience a higher median dose intensity, and have fewer dose reductions. Although not directly stated in the paper, this information together with a higher rate of hypertension in the axitinib arm suggests that upward dose titration of axitinib occurred successfully during the trial. Cessation of either therapy due to toxicity was uncommon, implying that toxicities were successfully managed in each arm. It appears unlikely that dosing problems, pharmacokinetic differences, or lack of familiarity with toxicity management could account for the negative results.

Could there have been other unsuspected differences between this trial population and that of the AXIS trial? ECOG performance status 1 patients comprised 43% of the AGILE study population, very similar to that of AXIS. Clinicians know that ECOG performance status can be a rough measure and a moving target. Performance status 0 is easy to define, as is 3 and 4. The difference between ECOG performance status 1 and 2 can be marginal and subjective. Could some patients of performance status 2 have been entered into the trial and designated as 1? A lack of other easily available options in some countries could increase the risk of this occurring, perhaps inadvertently or through lack of experience of some investigators. It is not possible to verify the performance status of the participants at study entry so this will remain an unanswered question.

In the end, we are left with two conclusions:

(I) Axitinib is active in this setting. The median PFS and toxicity profile are very respectable. Let us not make the mistake of thinking that this drug should not be developed in the first line setting;

(II) The study did not reach its primary endpoint. Either axitinib did not work as well as it was optimistically hoped, or sorafenib is a better drug now than it used to be. Clinical experience with this class of agents means that more patients can be kept on treatment or on appropriate doses and therefore that drugs like sorafenib are more likely to be used effectively. Perhaps this can account for the apparent improvement in the activity of sorafenib.

How can this trial inform us as we grapple with the unanswered issues listed at the beginning of this editorial?

(I) This trial allowed patients with "a clear-cell component". The paper does not provide the information, but it is probable that some participants had only a minor component of clear cell RCC. The same caveat applies to the AXIS trial and this is probably the case in routine clinical practice as well. Response rates in non-clear-cell histologies are low for VEGFR-targeted agents, however they do have activity particularly in the form of stable disease (17,18). Perhaps there is a rationale for an axitinib study in non-clear-cell RCC, if it is not to be developed further in the first line setting for clear cell RCC;

(II) Dose titration by toxicity is standard for axitinib. Why should this not be the case for other drugs? Could their apparent efficacy also be improved by similar personalised dosing (19)?

(III) The trial does not cast any further light on selection of post-first-line therapies. Extrapolation from the AXIS trial might suggest that other VEGFR-targeted therapies might be less effective after axitinib but this is not yet known;

(IV) It is still not known whether use of a more selective or a less selective drug is better for first line therapy. This trial has not answered the question. The COMPARZ trial, although it has been subject to criticism, has not demonstrated superiority of a more selective drug (pazopanib) over one with more off-target effects (sunitinib), so this remains an open question. It is plausible though that a drug with a narrower spectrum of activity might be a better first choice in that selection pressure for tumour escape will be primarily directed against those targets, in which case a drug with a broader spectrum of activity might still be active even if the VEGFR axis is less relevant at that time;

(V) Drug trial design and interpretation of their results need to take into consideration the local context. A possible reason for failure of the TIVO-1 trial was that patients randomised to sorafenib had the opportunity to receive two drugs sequentially on study, while those randomised to tivozanib were unable to cross to sorafenib and might have had no other options in the countries in which that trial was done (16). Access or lack of access to post-study therapies almost certainly will affect survival outcomes, and might alter the profile of patients recruited to these trials. In the case of tivozanib, the issues caused by the trial design have probably led to the demise of what seemed to be a very promising drug.

Where does this leave axitinib? It is an active and effective drug but its development has also been hampered by issues in trial design. It is unlikely now to be developed further as a first-line agent although this is probably exactly the setting where it might work best. It is active in the second line setting but clinicians still have no evidence to guide them as to whether their patients should receive it, everolimus, or another drug. Similarly, this trial has confirmed the activity of sorafenib, which for so long seems to have been considered as a form of "active placebo". Sorafenib clearly continues to have a role in the treatment of RCC. The future roles of these two agents and others such as sunitinib and pazopanib will be influenced by new developments such as effective immunotherapies.

Finally, I will join my voice with those of so many others: our ability to move the field ahead and to make rational treatment decisions for our patients will require development of reliable predictive biomarkers that will allow us to say confidently to our patients that a given choice of therapy is the best for them at that time.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research* for the series "Renal Cell Carcinoma". The article did not undergo external peer review.

Conflicts of Interest: IDD is an unremunerated member or chair of industry advisory boards for Pfizer, GlaxoSmithKline, Novartis, Bayer and Bristol Myers Squibb. All honoraria and remuneration for this work is paid directly to ANZUP Cancer Trials Group.

Ethical Statement: The author is 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. 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.
2. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125-34.
3. 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.
4. 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.
5. Escudier B, Bellmunt J, Négrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010;28:2144-50.
6. 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;28:1061-8.
7. 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.
8. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722-31.
9. Nicholaou T, Wong R, Davis ID. Tumour lysis syndrome in a patient with renal-cell carcinoma treated with sunitinib malate. Lancet 2007;369:1923-4.
10. 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;32:760-7.
11. 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;15:286-96.
12. Karaman MW, Herrgard S, Treiber DK, et al. A quantitative analysis of kinase inhibitor selectivity. Nat Biotechnol 2008;26:127-32.
13. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003;349:427-34.
14. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 2013;14:1287-94.
15. Rini BI, Garrett M, Poland B, et al. Axitinib in metastatic renal cell carcinoma: results of a pharmacokinetic and pharmacodynamic analysis. J Clin Pharmacol 2013;53:491-504.
16. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013;31:3791-9.
17. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. J Clin Oncol 2008;26:127-31.
18. Tafreshi A, Thientosapol E, Liew MS, et al. Efficacy of sorafenib in advanced renal cell carcinoma independent of prior treatment, histology or prognostic group. Asia Pac J Clin Oncol 2014;10:60-5.
19. Bjarnason GA, Khalil B, Hudson JM, et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: correlation with dynamic microbubble ultrasound data and review of the literature. Urol Oncol 2014;32:480-7.

Cite this article as: Davis ID. Axitinib in renal cell carcinoma: now what do we do? Transl Cancer Res 2014;3(6):562-566. doi: 10.3978/j.issn.2218-676X.2014.06.07

