Sequencing Systemic Therapies in Advanced RCC: Is There a Best Strategy?

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Overview

There is a strong rationale for sequencing targeted therapy in metastatic clear cell renal cancer. However, the timing of the switch and the best agent to switch to remains unclear. Randomized data currently are supportive of the sequence of axitinib, followed by everolimus in those patients in which first-line vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) therapy fails. Everolimus is also justified in the second-line setting, and the overall survival data for sorafenib in VEGF TKI-resistant disease is impressive. A degree of cross-resistance appears to exist between all these current agents and has resulted in a drive toward the development of new therapies with novel modes of action.

There are seven approved targeted agents for the treatment of metastatic clear cell renal cancer (RCC). These agents focus on two targets, which include the mammalian target of rapamycin (mTOR) and VEGF. Although there appears to be some cross-resistance between these two classes of agents, the reasons for this are unclear.

Randomized data (RECORD 1) showed mTOR inhibition notably delayed progression-free survival (PFS) compared with placebo after failure of VEGF-targeted therapy. This has driven the widespread use of sequential therapy in RCC. Before this study, sequencing of sorafenib and sunitinib was routinely used, driven by retrospective data and clinical experience. This led to a culture of switching therapy at progression of disease. Indeed, oncologists have developed a low threshold to change therapy, and patients are often exposed to multiple lines of therapy, including a rechallenge with the same agent.

Two years ago, a randomized phase III trial further supported the rational for switching one VEGF-targeted therapy to another. The AXIS study compared axitinib and sorafenib in patients in whom either sunitinib or immune therapy failed. Axitinib significantly delayed PFS in the patients in whom sunitinib failed (4.8 vs 3.4 months, p = 0.01). It is speculated that this is because axitinib is more potent at targeting VEGF receptors. However, the results with axitinib were more impressive in those patients who had not previously received VEGF tyrosine kinase inhibitor (TKI) therapy. There was no survival benefit with axitinib, despite the lack of crossover in the trial. Despite these issues, the AXIS data supports the use of axitinib after VEGF TKI therapy. The study also shows that subsequent therapies become increasingly less effective in RCC, following a “law of diminishing returns.” Today, randomized data support the use of both VEGF-targeted therapy and mTOR inhibitors in VEGF TKI-resistant disease. The lack of biomarkers to direct personalized therapy means there is no clear preferred choice between these two agents in this setting. The inherent differences between the trials and the differing mechanisms of action of the agents prohibit any meaningful comparison in efficacy and toxicity between axitinib and everolimus.

A more recent randomized phase III study (INTORSECT) has made the landscape more complex. This study compared temsirolimus (mTOR inhibitor) and sorafenib (VEGF TKI) in sunitinib-refractory metastatic RCC. Results showed there was no significant difference in PFS between these two agents; however, the sorafenib arm had significantly longer overall survival (4.3 months increase [12.3 months for temsirolimus vs. 16.6 months for sorafenib: p < 0.001]). Again, there was no crossover in this study. One could speculate that had this survival advantage been associated with a new trial drug in RCC, and not sorafenib, it would be seen as a major breakthrough. These data raise two major issues which need to be addressed in detail: first, is PFS a good surrogate marker for outcome in VEGF TKI-refractory RCC and second, is continued VEGF-targeted therapy required to maximize outcome?

PFS as Endpoint in VEGF-Refractory Disease

The breakdown in the relationship between PFS and overall survival in the INTORSECT study requires particular attention. The reason for the breakdown is unclear, but factors such as immunologic effects of agents or subsequent...
therapies may play a role.\textsuperscript{9} PFS has been used for the registration approval of all agents in the VEGF TKI-refractory setting in RCC.\textsuperscript{3,6} PFS, determined by RECIST criteria, is radiologically precise but may be less robust in determining treatment failure, potentially making it clinically less relevant.\textsuperscript{7} A combination of clinical factors and radiologic factors are used in other tumors such as prostate cancer, which may be useful in RCC in the future. An issue is whether PFS should be used as the primary endpoint of future trials. Importantly, the most recent randomized phase III study in this setting (comparing PD-1 inhibitors and mTOR-targeted therapy) is using overall survival as the primary endpoint.

**WHEN TO SWITCH THERAPY IN CLINICAL PRACTICE**

Clinical trial data support the use of active therapy at disease progression and switching from one VEGF-targeted therapy to another is well established.\textsuperscript{3,6,8} The timing of the switch, however, has never been tested. Radiologic assessment by RECIST dictates that the development of as little as one new disease-related lesion defines disease progression. This often occurs in the face of what is felt to be ongoing clinical benefit.\textsuperscript{11} In routine clinical practice, using a more complete clinical assessment may be considered, and an immediate switch at RECIST progression may not be required. Other factors such as the burden of disease, the sites of tumor growth, and changing prognostic factors could be assessed. It is conceivable that switching from more potent VEGF targeted therapies (such as tivozanib) to less potent agents (such as sorafenib) may even be counterproductive. Therefore, careful consideration should be used before a switch occurs.

**BIOMARKERS TO DETERMINE SUBSEQUENT THERAPIES**

Forest plot analysis was unable to identify specific factors associated with clinical benefit in AXIS or the INTORSECT study.\textsuperscript{6,8} Specifically, those patients who did not responded well to first-line VEGF-targeted therapy did not appear to benefit from switching the mode of action to mTOR. These results are particularly disappointing as we are no further forward in selecting between VEGF-targeted therapy and mTOR inhibitors for individual patients.

Prospective data shows single nucleotide polymorphisms (SNPs) to VEGF receptors may be able to differentiate patients who benefit from axitinib rather than sorafenib.\textsuperscript{6} Further data in this area is required. This type of analysis using blood or germ-line material is perhaps the most promising area for a breakthrough as it is easily collected and reproducible.

**ARE TARGETED THERAPIES FROM THE SAME CLASS OF DRUG THE SAME?**

There is a plethora of data showing pharmacokinetic and pharmacodynamic differences between VEGF TKI therapy, which is largely because of distinct “off-target” effects and different potency of VEGF targeting. This translates into differences in efficacy and toxicity profiles.\textsuperscript{11} Indeed, randomized data (the EFFECT study) with sunitinib shows that even the dosing of the same agent can potentially influence both toxicity and activity.\textsuperscript{12}

The differences between temsirolimus and everolimus are more subtle. The drugs have identical metabolites, although this process of metabolism is different. The mode and frequency of administration are also different. Therefore the assumption that clinical trial results with different mTOR inhibitors are interchangeable is flawed.

**THE EFFECT OF NEW AGENTS ON SEQUENCING**

In the near future, a pivotal third-line study comparing dovitinib (a VEGF- and FGF-2-targeted therapy) and sorafenib in patients whose disease progressed through first-line VEGF-targeted therapy and second-line mTOR inhibition will report results (the GOLD study). PFS is the primary endpoint of this study. In view of the issues with AXIS and INTORSECT, many clinicians may wish to see an overall survival signal as well as a PFS signal before adopting this approach as standard of care. A positive study may redress the balance, which currently is tipping toward continued VEGF TKI therapy in the second-line setting.

Recent phase I results with a PD-1 inhibitor were assessed and the drug was moved straight into a phase III setting in VEGF-refractory metastatic RCC.\textsuperscript{13} Overall survival is the primary endpoint of this study. However, it is speculated that immune therapy is more effective earlier in the disease process. Also, VEGF targeting has an immunological component in its own right, which may have an effect on biomarker expression and response.\textsuperscript{9} Nevertheless, results of this study are eagerly awaited.

**TOXICITY IN DETERMINING SEQUENCE OF TARGETED THERAPY IN RCC**

mTOR inhibitors and VEGF-targeted therapies have very distinct toxicity profiles.\textsuperscript{3,6} Therefore, switching the mode of action in patients who have encountered particular problems with previous VEGF therapies in the first-line setting would appear logical. This may be one of the most compelling reasons for choosing subsequent therapies in subgroups of patients.
TREATMENT FOR PATIENTS WHO DO NOT RECEIVE FIRST-LINE VEGF-TARGETED THERAPY

There is a lack of data on the subsequent treatment of poor-risk patients in whom first-line temsirolimus fails. These patients have a short median survival, however, VEGF-targeted therapy in the second-line setting appears clinically justified despite the lack of data. Even today, a small proportion of patients are given first-line immune therapy (interferon or IL-2). Data with axitinib in these patients (from the AXIS study) appears particularly impressive.6

SUMMARY
Overall, there is strong rationale for sequencing of VEGF-targeted therapy, although the exact timing of the switch and the best agent to switch to remains unclear. There are genuine questions regarding the survival advantage associated with switching therapy, compared with continuing with existing therapy regardless of progression. Randomized data currently support the sequence of axitinib, followed by everolimus in patients in whom first-line VEGF TKI therapy failed. Everolimus is also justified in the second-line setting, but if given as a second-line therapy, subsequent third-line treatment then becomes challenging based on current evidence. The GOLD study may address this. Finally, the overall survival data for sorafenib in VEGF TKI-resistant disease is impressive in all the randomized studies. A degree of cross-resistance appears to exist between all these current agents and is resulting in a drive toward the development of new therapies with novel modes of action (PD/PDL-1 and FGF-2 inhibition).

Disclosures of Potential Conflicts of Interest

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References