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Treating advanced kidney cancer—miles to go before we sleep

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Abstract

A randomized phase III trial comparing pazopanib with sunitinib in patients with advanced clear cell renal cell carcinoma showed that although progression-free survival and overall survival were similar, pazopanib was better tolerated. Recent advances in genomics and metabolomics have provided novel insights that could be leveraged to improve therapy.

In a recently published multicentre, phase III randomized trial (COMPARZ) in 1,110 patients with metastatic clear cell renal cell carcinoma (ccRCC), Motzer *et al.*¹ compared the efficacy and safety of pazopanib and sunitinib, two multiple tyrosine kinase inhibitors (TKIs) with activity against the vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptor (PDGFR). Patients were randomly assigned to receive either pazopanib (800 mg once daily; $n = 557$) or the standard sunitinib regimen (50 mg once daily for 4 weeks followed by 2 weeks with no treatment; $n = 553$). The primary end point was progression-free survival (PFS) and the study was designed to evaluate noninferiority of pazopanib compared with sunitinib. Secondary end points included overall survival, quality of life and safety. Median PFS in patients treated with pazopanib was 8.4 months compared with 9.5 months for sunitinib. On the basis of predefined criteria, pazopanib was determined to be noninferior to sunitinib (hazard ratio [HR] for PFS 1.05, 95% CI 0.90–1.22). Overall survival was comparable in the two groups, with a median of 28.4 months in the pazopanib group versus 29.3 months in the sunitinib group (HR 0.91, 95% CI 0.76–1.08).

Despite these similarities, differences were noted in the adverse event profile and patient tolerability between the two groups. Patients treated with sunitinib had a higher incidence of fatigue (63% versus 55%), thrombocytopenia (78% versus 41%) and hand–foot syndrome (50% versus 29%), whereas increased levels of alanine aminotransferase were more common in the pazopanib group (60% versus 43%). Quality-of-life assessments related to fatigue or soreness in the mouth, throat and hands or feet during the first 6 months of treatment favoured pazopanib.¹

Results from another, smaller study evaluating patient preference between pazopanib and sunitinib (PISCES, NCT01064310), were reported at the ASCO annual meeting in May

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Competing interests

The authors declare no competing interests.

2012; approximately 70% of patients reported that pazopanib was more tolerable and indicated a preference for this agent over sunitinib based solely on tolerability. Although these and similar studies are an important step in our ability to optimally manage patients with ccRCC and will likely influence our choice of first-line agents in this patient population, little progress has been made in our efforts to significantly improve both PFS and overall survival observed with the first targeted agents introduced over 7 years ago.

The rationale for targeted therapy for this cancer dates back 20 years, to the identification of the *VHL* gene, which is inactivated by mutation or methylation in >90% of cases of sporadic ccRCC.² Understanding the signalling pathway effects of its gene product, the von Hippel–Lindau tumour suppressor (VHL), provided the foundation for the development of targeted therapy on the basis of the role of the VHL protein complex in regulating the cellular response to hypoxia. The VHL protein is part of an E3 ligase complex, which includes elongin C, elongin B, Cul2 and Rbx1. This complex targets the α -subunit of hypoxia inducible factor (HIF)-1 and HIF-2 by way of ubiquitin-mediated degradation in the presence of oxygen. Under low-level oxygen (that is, hypoxia), the VHL complex cannot target and degrade HIF, resulting in HIF accumulation and activation of numerous downstream transcriptional targets, such as VEGF, PDGF and EGF.

Although seven therapeutic agents targeting the VHL pathway—bevacizumab, sunitinib, pazopanib, sorafenib, axitinib, everolimus and temsirolimus—have been approved as either first-line or second-line therapies for patients with advanced-stage renal cell cancer (Figure 1), we still have a long way to go. Complete response is rare and most patients' tumours eventually progress and they succumb to their disease. Why are we not doing better? One possible reason is that we are currently only targeting a small number of downstream HIF targets (that is, up-regulated growth factors and their respective receptors). It is possible that direct targeting of HIF-2, for example, might provide a more-effective approach.

Another possibility is that we are ignoring other aspects of ccRCC that will need to be targeted to achieve maximal therapeutic efficacy. Metabolomic studies as well as expanded next-generation genomic sequencing and large-scale multiplatform integrated analyses have highlighted several new potential targets and approaches to therapy for ccRCC. Beginning with the sequencing-based reports from Dalglish *et al.*³ and Varella *et al.*⁴—and highlighted by two recent integrated analyses from The Cancer Genome Atlas (TCGA) Research Network⁵ and Sato *et al.*²—mutations of chromatin remodelling genes, including *PBRM1*, *SETD2* and *BAP1* have been identified in a high percentage of ccRCC cases. Mutations of *SETD2* and *BAP1* correlate with cancer-specific survival, suggesting a role in disease progression and with implications for therapeutic intervention.⁶ Studies are currently underway to understand the effects of these modifications to chromatin remodelling function to identify additional approaches to therapy.

In addition to the chromatin remodelling gene findings, recent studies have shown that kidney cancer is fundamentally a metabolic disease.⁷ Metallo *et al.*⁸ reported that VHL-deficient kidney cancer is characterized by reductive glutamine metabolism for lipid biogenesis, a mechanism very similar to that described in fumarate hydratase-deficient kidney cancer.⁹ In addition, in the comprehensive integrated analysis of ccRCC performed

by the TCGA Research Network, high-grade, high-stage tumours from patients were found to have undergone a Warburg-like metabolic shift to aerobic glycolysis, with indications of impaired tricarboxylic acid cycle function.⁵ These findings suggest that a number of potential therapeutic approaches targeting glucose transport and glycolysis as well as the glutamine and antioxidant response pathways might be useful for treatment of advanced-stage ccRCC.

In summary, new phase III data suggest that pazopanib is likely to be increasingly used as a first-line option in patients with metastatic ccRCC, based on its noninferior efficacy, but superior tolerability profile compared with sunitinib. In addition to strategies to improve tolerability and optimal sequencing of available targeted agents, future efforts focusing on the development of novel strategies to target newly identified genetic and metabolic aberrations in ccRCC will hopefully lead to the development of more-effective forms of therapy for patients with this disease.

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Pull quotes

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Targeting VHL/HIF in Clear Cell RCC

Figure 1.

The seven FDA-approved agents for the treatment of kidney cancer targeting the von Hippel–Lindau (VHL) tumour suppressor pathway.