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Editorial Comment

Renewed hope for patients with advanced renal cell cancer: Cinderella comes of age

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Patients with advanced renal cell cancer have had few attractive options to date. Despite many years of scientific research and clinical investigation, the mainstay of treatment remains immunotherapy with interferon-alpha or interleukin-2. Many questions remain as to the optimum treatment regimen. What is clear is that the majority of patients experience considerable side-effects but little benefit. Response rates are in the region of 10–20% and the effect on median survival is around 4 months. Clearly there is a desperate need for improved treatment. However, this bleak picture is likely to change soon for three reasons: first, years of painstaking research have revealed parts of the molecular pathogenic pathways responsible for renal cell cancer; secondly, new agents are reaching the clinic that have the potential to translate this molecular knowledge into patient benefit; and thirdly, there is renewed interest in selecting the most appropriate treatment for patients with one of the varieties of renal cell cancer. These issues were discussed recently at the First International Conference on Innovations and Challenges in Renal Cancer [1].

1. Molecular pathogenesis

The most common genetic abnormality in renal cell cancer is mutation or hypermethylation of the von-Hippel Lindau (*VHL*) gene, which is present in around 60% of clear cell tumours. Normally *VHL* regulates the stability of hypoxia-inducible factors (HIF). Inactivation of *VHL* results in high levels of HIF and its downstream targets vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and tumour growth factor-alpha (TGF-α). Overexpression of these factors leads to angiogenesis, cell survival and proliferation. In part these effects are mediated by the Ras/Raf/MEK/ERK and phosphoinositide 3-kinase (PI3K)/Akt pathways, as shown in Fig. 1. Elucidation of these pathways has revealed several potential therapeutic targets in renal cell cancer. The most exciting aspect of these findings is that many agents are in development to target these pathways and there is considerable interest from the pharmaceutical companies in developing treatments for this erstwhile Cinderella of oncology.

2. Therapeutic signals

The list of new agents under investigation in renal cell cancer includes bevacizumab to inhibit VEGF, epidermal growth factor receptor (EGFR) antagonists such as erlotinib, CCI779 to inhibit mammalian target of rapamycin (mTOR) and, perhaps with most promise at present, the multi-targeted kinase inhibitors BAY43-9006 and SU11248. All of these agents have been investigated as single agents and the next stage is to combine them either vertically (blocking the same pathway at multiple points) or horizontally (blocking several different pathways at the same time). In this edition of the *European Journal of Cancer* D'Hondt and colleagues [2] elegantly outline these various studies.

The kinase inhibitors have progressed rapidly through phase I and II trials and two agents are now in phase III, BAY43-9006 in the second-line setting and SU11248 in the first-line setting. It has been assumed that vascular endothelial growth factor receptor 2 (VEGFR2) is the major target of these agents, although there is no conclusive indication of this to date. Much has been learnt in a short time. Disease

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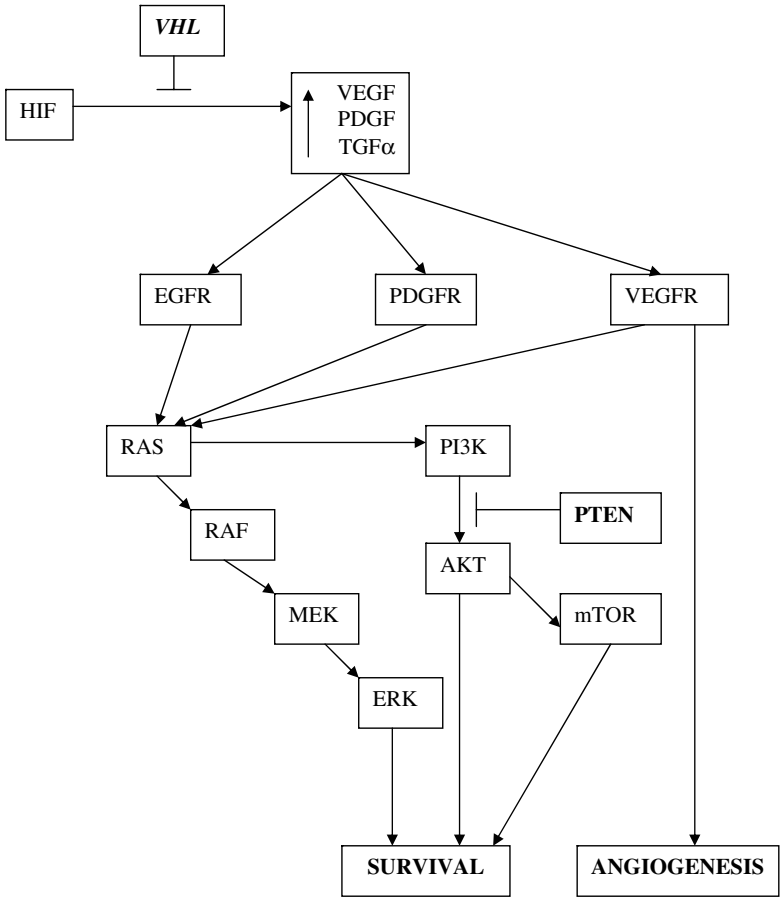

Fig. 1. Key signalling pathways in renal cell carcinoma. VHL, von-Hippel Lindau; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; TGF-α, transforming growth factor-alpha; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; mTOR, mammalian target of rapamycin.

stabilisation is a major feature of kinase inhibition in renal cell cancer, often lasting in excess of a year. Although disease shrinkage is seen in around 60% of patients this often does not reach the standard definition of partial response and there is no record of a complete response to date. One notable feature of response is the development of low attenuation on computed tomography (CT) scan in the middle of tumour masses. This has been ascribed to central necrosis, although direct evidence for this is lacking. It is interesting to note that similar features may be seen in the treatment of gastrointestinal stromal tumour (GIST) with imatinib. In both cases the lesions may swell on the development of central low attenuation and it is important not to mistake this for progression.

In assessing the merits of kinase inhibitors it seems that duration of benefit may be at least as important as degree of tumour shrinkage. In the case of BAY43-9006 the side-effect profile improves as patients are maintained on the drug, although the reasons for this are not known. It is possible that this is due to changes in drug absorption or metabolism or in receptor population. Whatever the cause, dose escalation is often possible and this may prove important in optimising the duration of benefit for patients.

3. Treatment selection

The pendulum has truly swung away from immunotherapy. However, it is important to remember that whilst no complete responses have been seen with kinase inhibitors or any of the new agents, they are a well-recognised, although sadly uncommon, feature of immunotherapy. It is fascinating that progress has been made recently in identifying markers that may predict for response to immunotherapy. Immunotherapy is likely to remain an option for patients with advanced renal cell cancer whose marker profile suggests a high chance of success.

The therapeutic target(s) for multi-targeted kinase inhibitors are not clear but interest has focused around *VHL* and its modulation of the VEGFR, platelet-derived growth factor receptor (PDGFR) and

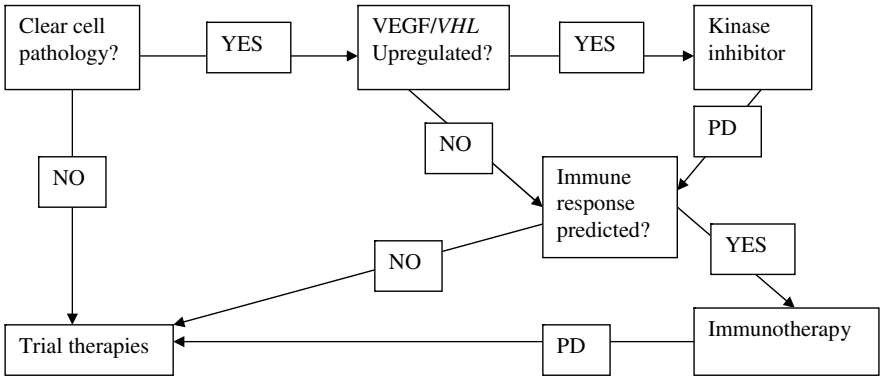

Fig. 2. Speculative future treatment paradigm for advanced renal cell cancer. VEGF, vascular endothelial growth factor; *VHL*, von-Hippel Lindau.

EGFR signalling pathways. It is not possible to exclude a role for the Ras/Raf/MEK/ERK pathway but it is important to note that, unlike in melanoma, no *BRAF* mutations have been found in renal cell cancer. It must be a distinct possibility that we will be able to select kinase inhibition as a treatment option for patients whose tumours show dysregulation of specific pathways. Thus it becomes possible to glimpse the outlines of a treatment paradigm for patients with advanced clear cell renal cancer (Fig. 2). The picture remains much less clear for the substantial minority of patients with papillary or other non-clear cell histologies. Nevertheless, progress in the last 3 years has been remarkable and there is now the prospect of the first effective and well-tolerated treatments for the majority of patients with advanced renal cell cancer. Cinderella is about to come of age.

References

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