New prognostic models in metastatic renal cancer

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Currently 7 targeted therapies have been approved for the treatment of advanced RCC: sorafenib, sunitinib, temsirolimus, axitinib, bevacizumab in combination with interferon-α, everolimus and pazopanib (1). There is difficulty distinguishing between them due to lack of head to head studies. Therefore there are multiple treatment options for patients in the first and second line setting.

Due to clinical trial design, specifically cross-over and the influence of subsequent therapies, few of these drugs have proven overall survival benefit compared to the control arm (2,3). Despite this, the development of targeted therapy has increased survival in metastatic renal cancer approximately 2 fold (2,4).

There is huge variation in outcome to targeted therapy within the patient population. This is coupled with a lack of biomarkers to predict response and inadequate detail on the biological mechanisms of drug failure. Sophisticated imaging and biomarker analysis have not proved helpful in the identification of patients who might benefit from treatment (5). Therefore one could argue we have made very little progress in the drive towards personalized medicine and only identified new hurdles, such as tumour heterogeneity (6). Moreover evidence suggests that targeted therapy results in dynamic changes to the tumor which may partly explain why predictive markers from archived tissues may not be relevant in the relapsed setting (6).

The field may be becoming more complex as established endpoints such as response and even progression free survival may not correlate with overall survival. To illustrate this, the most recent 2nd line study, comparing VEGF TKI therapy with mTOR inhibition in sunitinib refractory RCC, shows that while there is no difference in progression free survival patients on mTORs had a shorter survival (7).

It is unlikely that this will become any more straight forward in the future, as the responses seen with newer immune therapies such as PD-1 appear unpredictable (8). It is conceivable that established benchmarks such as RECIST which is used to be used to measure progression may become redundant with these new agents.

Therefore the identification of new predictive markers is the next big step in renal cell carcinoma.

From this article recently published in Lancet Oncology (9), five candidate angiogenic factors were measured for their prognostic significance in patients with metastatic renal cancer treated with pazopanib. The randomization of patients against placebo allowed for the investigation of predictive markers as well as prognostic markers. They used a 3 step approach with a screening phase, conformation and validation phase. In the pazopanib treated group, high baseline levels of interleukin 8, osteponitin, hepatocyes growth factor (HCG) and tissue inhibitor of metalloproteinases (TIMP)-1 were associated with a shorted progression free survival. Further analysis showed different spectrum of prognostic plasma makers seen with placebo. These differences suggest that the targeted therapy is associated with distinct molecular profiles which are of prognostic relevance. In this manuscript, the prognosis of the cytokine expression appears more significant than other prognostic models such as Heng prognostic scores and is therefore a step in the right direction. Unlike standard clinical classifications, however some plasma markers were also predictive of greater relative benefit from pazopanib. For example patients with increased levels of cytokines especially interleukin 6 had a worse prognosis but a greater relative benefit from pazopanib. Although this study provides evidence that plasma markers can identify patients who receive greater relative benefit from pazopanib (as compared with placebo) it would indeed be interesting to see whether these marker would predict benefit from other treatment types e.g., mTOR inhibitors.

The findings from these studies support the approach of the use of cytokine and angiogenic factor (CAF) profiling to define biologically distinct subgroups of patients with metastatic renal cell carcinoma whose tumours have a greater angiogenic drive. CAF profiling might also be particularly well suited for angiogenesis inhibitors and other drugs targeting the tumour micro-environment, in which both circulating host derived and tumour derived factors could affect response.

Another possibility is to investigate dynamic changes to cytokines from sequential plasma, as this may better define a responding population. Finally, the integration of these prognostic and predictive factors with other significant factors such as single nucleotide polymorphisms may increase the power of these models (10). Powerful models predicting which patients benefit from specific agents is likely to be more useful than the development of further similar VEGF TKI therapies.

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Footnote

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