Review Article

Biomarkers for tyrosine kinase inhibitors in renal cell cancer

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Introduction

Renal cell carcinoma (RCC) is a common malignancy. In 2012, in the USA, there were 65,000 new cases and 13,500 disease-specific deaths. In the same year it was the 6th most common new cancer diagnosed (1). During the last 50 years, despite an increase in incidence, the mortality has fallen, a possible result of earlier detection and improvements in therapy (2).

Traditionally, renal cell cancer has proven refractory to cytotoxic therapies, and for many years immunotherapy was the standard of care, even though it was not particularly effective. Over the past decade, the molecular biology behind renal cancer development has been better understood and subsequently a number of targets have been identified for potential therapies (3).

Mutations in the tumour suppressor Von Hippel-Landau (VHL) gene are responsible for the majority of cases of sporadic clear cell renal cell carcinoma. VHL mutations result in aberrant binding of hypoxia-inducible factor 1 (HIF1) subunits which translocate to the cell nucleus and result in transcriptional activation of a number of factors necessary for angiogenesis, including the vascular endothelial growth factor (VEGF) (4). Efforts directed towards inhibiting neoplastic neoangiogenesis, via the VEGF or the mammalian target of rapamycin (mTOR) pathways (5), have yielded positive results with clinical benefit.

To date, four tyrosine kinase inhibitors (TKI's) have been shown to benefit patients in phase III randomized controlled trials: sunitinib (6), sorafenib (7), pazopanib (8) and axitinib (9). Similarly, randomized data has also supported the use of the mTOR inhibitors temsirolimus (10) and everolimus (11). Despite these encouraging data, improvements in progression free survival (PFS) and overall survival (OS) have been measured in months, and not all patients have benefited uniformly. Hence a need exists to develop robust biomarkers for renal cancer that will help direct therapy in patients destined to do either very well or poorly.

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (12). Biomarkers serve an important role in oncology. They can assist in diagnosis, screening, prognosticating and as measures of response to certain therapies (4,13). A prognostic biomarker is able to estimate the chance of disease recurrence or death, regardless of any intervention (14). Conversely, a predictive factor is one which assists in predicting the probability of a response to a certain therapy (4). Predictive markers can provide information about the effect of a particular treatment, or serve as a target of a particular intervention (14). Identifying predictive biomarkers can therefore identify patients most likely to benefit from certain treatments. This maximizes efficacy and minimizes unnecessary exposure of patients to toxic therapies for which they are destined to derive no benefit.

As the molecular understanding of the pathogenesis of renal cell carcinoma has grown, a number of potential predictive markers have become apparent. In this review, we describe the predictive factors related to each of the tyrosine kinase inhibitors that are presently available for the treatment of metastatic renal cell carcinoma. Due to space constraints, we will consider only molecular biomarkers.

Sunitinib

Sunitinib is an tyrosine kinase inhibitor targeting VEGF receptors-1, -2, -3, platelet-derived growth factors, KIT, FLT-3, colony-stimulating factor-1 receptor and RET (15). The pivotal phase III trial of treatment-naive patients

with metastatic RCC showed significant improvements in response rate, progression-free and overall survival (16) with similar results confirmed in an expanded-access trial of over 4,000 patients (17). However, not all patients respond to sunitinib and some develop significant toxicities resulting in dose delays, reductions or discontinuations. There is emerging evidence for the importance of maintaining suninitib exposure in maximising efficacy (18), and therefore potential biomarkers are needed to identify patients who will most likely benefit or develop significant toxicities.

Single nucleotide polymorphisms (SNPs) have been investigated as potential biomarkers, particularly in angiogenesis and drug metabolising genes such as *CYP3A4*. In a prospective pharmacogenomic study of 101 patients with advanced clear cell RCC, Garcia-Donas and colleagues (19) reported two VEGFR3 missense polymorphisms (rs307826 and rs307821) that were associated with a reduced PFS with sunitinib use (HR 3.57 and 3.31 respectively). The authors also discovered that the CYP3A5*1 (rs776746) high metabolising allele was associated with increased dose reductions due to toxicity (HR 3.75). Several smaller studies have reported associations between genetic variants in *VEGF* and *VEGFR2* (20), *CYP3A5*, *NR113* and *ABCB1* genes (21) and outcomes. A large prospective multinational trial, of which 75% of the 219 enrolled patients had metastatic renal cell carcinoma, identified variants in *CYP1A1*, *ABCB1*, *ABCG2*, *NR113*, *VEGFR2* and *FLT3* genes that were associated with toxicity from treatment with sunitinib (22). A retrospective study of 135 patients (65 who received sunitinib) examined the associations between four molecular markers (HIF-1α, CAIX, PTEN and p21) determined by immunohistochemistry and outcomes from treatment. CAIX overexpression was associated with more responses to newer targeted agents (64.7% versus 21.1%). High PTEN and low P21 expression were associated with an improved response to sunitinib (23).

Several plasma markers have been investigated for their role in predicting clinical outcomes, including those involved in angiogenesis such as VEGF and VEGF-related proteins, placental growth proteins, SDF-1, sVCAM-1 (24-28) and cytokines (29). Rini and colleagues [2008] reported the value of baseline sVEGFR-3 and VEGF-C as potential biomarkers of PFS and RR (28). Several small prospective studies have shown that sunitinib therapy leads to modulation of circulating proteins involved in VEGF signaling. In these studies, significant changes in VEGF, sVEGFR-2, sVEGF3, PDGF and SDF-1 between baseline and either day 14 or 28 led to associations with RR, PFS and OS (24,26). TNF-alpha and MMP-9 were identified as potential biomarkers of sunitinib activity in a study of 31 patients. Five candidate cytokines (TNF-alpha, MMP-9, ICAM-1, BDNF and SDF-1) were evaluated and elevated levels of TNF-alpha and MMP-9 were associated with reduced PFS and OS (29).

Emerging evidence suggests that circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs) may be promising as potential biomarkers with sunitinib treatment. Several studies have examined the dynamics of CECs with sunitinib treatment, and suggested significant CEC increases during treatment represent the targeting of immature tumour vessels (30) and are associated with improved PFS (31). Conversely, Farace and colleagues [2011] found no association between baseline changes in CECs and PFS or OS (24). The role of CEPs are unclear, however studies have shown an increased recruitment of these cells and haematopoietic progenitor cells into the neoangiogenic perivasculature, playing an important role in events necessary for tumour invasion and metastasis (24). Although promising, the reliability and sensitivity of measurements of CECs and CEPs using flow cytometry remains an issue and may limit its use in the research setting and application in clinical practice.

Sorafenib

Sorafenib is a tyrosine kinase inhibitor targeting serine/threonine kinase Raf-1 (Wilhelm *et al*., 2004) and VEGFR, platelet-derived growth factor receptor receptor β (PDGFR-β), c-KIT, RET, and FLT-3 (32,33). Sorafenib is able to directly affect tumor cell proliferation as well as angiogenesis (34).

A randomized Phase II study of sorafenib with or without interferon alfa-2b (35) showed no particular benefit of the combination, though it is likely the study was underpowered, as only 80 patients were randomized. Nevertheless, increased pAkt predicted for poorer progression-free survival and overall survival.

In the pivotal Phase III treatment approaches in renal cancer evaluation (TARGET) trial, 903 previously treated RCC patients were randomly assigned to sorafenib or placebo. In the final analysis reported by Escudier *et al.* (7), OS was not different between patients in the sorafenib or placebo arm, though when post cross-over effects were excluded, OS did continue to favour sorafenib (HR 0.78, P=0.029). In that study, baseline VEGF levels were prognostic for both PFS and OS. In a further subset

biomarker analysis of that study, a number of biological markers were found to be prognostic for survival: VEGF, carbonic anhydrase IX (CAIX), tissue inhibitor of metalloproteinase 1 (TIMP-1), and Ras p21 levels. Of these, only TIMP-1 was found to be independently prognostic in multivariate models (36). However, VHL mutational status was not related to sorafenib benefit.

Pazopanib

Pazopanib is an oral tyrosine kinase inhibitor that received FDA approval in 2009 for the treatment of metastatic renal cell carcinoma. It binds to VEGF receptor-1, -2 and -3, platelet derived growth factor (PDGF) receptor -α and -β and c-kit receptors (37). In a phase III study published in 2010, 435 patients with metastatic renal cell carcinoma, half of who had previously received cytokine treatment, were randomised to placebo or pazopanib. The pazopanib arm was associated with a superior progression free survival (9.2 *vs.* 4.2 months, P<0.0001) and a better overall response rate 30% *vs.* 3% (P<0.0001) (8).

Xu and colleagues (38) tested their hypothesis that genetic polymorphisms are associated with differing clinical responses to pazopanib. 27 polymorphisms, known to affect angiogenesis, metabolism or the mode of action of pazopanib were identified and retrospectively tested in 397 patients previously enrolled in pazopanib *vs.* placebo clinical trials. Polymorphisms in interleukin 8 (IL-8) and HIF1A were associated with a significantly poorer progression free survival compared to the wild type form (27 *vs.* 48 weeks, P=0.01 and 20 *vs.* 44 weeks, P=0.03 respectively). Inferior response rates were noted in patients expressing variant HIFA, NR1I2 and all three subsets of the VEGF gene. Similar associations between PFS and variant IL-8 and HIF1A were not seen in those patients treated with placebo, and hence these polymorphisms were considered to be predictive biomarkers.

These findings have biological merit; IL-8 is up regulated in murine models exposed to another TKI, sunitinib, and provides an alternative pathway to angiogenesis and drug resistance (39). Variant forms of HIF1A are known to provide endothelial cells with a greater capacity for angiogenesis (40), and ability to overcome the antineoplastic activity of pazopanib.

Recently, Tran *et al.* (41) examined the predictive and prognostic utility of circulating cytokine and angiogenic factors (CAF's) in patients with metastatic renal cell carcinoma treated with pazopanib. A small number of biomarkers were selected and then determined in stored serum from patients involved in the earlier pazopanib phase II and III clinical trials. Using a systematic process, these biomarkers were tested in the phase II study, and then validated in the larger phase III trial. Although high concentrations of IL-6, IL-8 and osteopontin were prognostic, only IL-6 demonstrated greater benefit relative to placebo. In the placebo arm, an elevated level of IL-6 above the median (relative to below the median) was associated with a statistically superior PFS of 9.9 *vs.* 24 months (P<0.0001). Although a difference also existed in the pazopanib group, it was no longer statistically significant (33 *vs.* 42 months, P=0.445). The authors concluded that high levels of IL-6 were predictive of PFS benefit with pazopanib. Similar results were not noted for overall survival, a likely consequence of the high level of cross over in the original phase III trial.

Aiming to validate these findings, Liu *et al.* (42) retrospectively re-tested a selection of biomarkers from patients in the original phase III trial and again found IL-6 to be predictive of an improved PFS in patients treated with pazopanib. IL-6 has been described as an independent predictor of poorer survival in metastatic renal cancer as early as 2004 (43) and has also been implicated in the paraneoplastic manifestations of the disease, including fever, weight loss and anaemia (44).

In a retrospective study presented in an abstract form in 2008, low levels of serumVEGF-2 correlated with response rate in patients with metastatic renal cancer treated with pazopanib (45). In a separate pre-clinical study, a nuclear medicine tracer linked the VEGF receptor was shown to provide evidence for early tumour regression in murine models treated with pazopanib (46). Such a tracer may allow for an immediate assessment of anti-tumour efficacy and provide much more timely information than standard radiological evaluation. The lack of a placebo control in these two studies make it difficult to conclude that these biomarkers are indeed predictive for outcome.

Temsirolimus and everolimus

The mammalian target of rapamycin (mTOR) pathway has become a successful target for two new FDA approved agents in renal cancer, Temsirolimus and Everolimus. Two Phase III trials have established a benefit of these agents either used first line in poor risk patients or following treatment with a tyrosine kinase inhibitor (10,47).

The advanced renal cell carcinoma (ACRR) trial

randomized treatment-naïve patients to temsirolimus, interferon-α (IFN) or a combination. Patients receiving temsirolimus alone experienced a progression free survival and overall survival benefit compared to IFN-α or the combination arm (10). Tumour samples in this study were assessed using immunohistochemistry for a range of potential molecular markers including HIF1α, HIF2α, phosphorylated Akt (pAkt) and phosphatase and tensin homolog (PTEN). In the single treatment arms, data was assessed in only 50% of patients for HIF1α and PTEN and not at all for pAKT and HIF2α. Neither baseline PTEN nor HIF1α levels were found to be of predictive value (48). In an explanation for this, the authors cited a number of logistical issues (poor tissue availability and an inability of immunohistochemistry to detect subtle biomarker quantities), which made this type of analysis difficult to perform.

Cho *et al*. assessed baseline levels of carbonic anhydrase IX (CAIX), phosphorylated S6 (pS6), pAkt and PTEN in tumour specimens from 20 patients receiving temsirolimus in a phase II trial. Patients with increased expression of pS6 were more likely to have a clinical response. Although a similar trend was found for pAkt, this did not reach statistical significance (49). These biomarkers deserve further study to establish if they are of predictive value in patients receiving treatment with an mTOR inhibitor.

Lactate dehydrogenase (LDH) has prognostic significance in RCC. Elevated levels of LDH are associated with reduced OS, and as such are widely incorporated into prognostic models (50-52). Retrospective analysis of the ARCC trial found that pretreatment LDH levels (>1× upper limit of normal (ULN)) were associated with an adjusted hazard ratio (HR) for death of 2.81 (P<0.001). For patients with an elevated LDH (>1× ULN), OS was improved in the patients receiving temsirolimus compared to IFNα with a HR for death of 0.56 (P=0.002) with no difference found in patients with a low LDH (53) .

Axitinib

Axitinib is an oral tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptors (VEGF) 1, 2 and 3 (54). It binds with increased affinity to VEGF-2, thereby differentiating it from other TKI's (55). In addition to activity in renal cell cancer, Axitinib has demonstrated efficacy in thyroid, breast, non-small-cell lung cancer cancer (56-58). The phase III AXIS trial randomized 723 previously treated patients to either Axitinib or Sorafenib (9). Axitinib was associated with a PFS benefit of 6.7 *vs.* 4.7 months (P<0.0001) and was subsequently approved by the FDA in early 2012. The role of Axitinib as a second line therapeutic option however, is not clearly defined given the positive results of everolimus also in the second line setting (47).

Given its relatively recent history, there are comparatively few published studies regarding predictive molecular biomarkers for axitinib. In a phase I study conducted by Mukohara *et al*. (59), 12 patients were administered Axitinib in escalating doses. Axitinib exposure correlated inversely with the concentration of soluble growth factor receptor 2 (s-VEGFR2), This observation appeared to be a function of drug concentration and was not predictive of efficacy. The association between s-VEGF2 and Axitinib was further explored in a phase I study conducted by Tomita *et al*. (60). A PFS benefit existed for those patients with s-VEGF-2 concentrations below the median (13 *vs.* 9 months, P=0.01). Although these results were interesting, this trial was not placebo controlled, and therefore could not conclusively prove that s-VEGF2 is a predictive marker.

Conclusions

At the present time there is no prospectively validated predictive or prognostic biomarker to help guide treatment selection decisions for which patients might most benefit from therapy with one tyrosine kinase inhibitor over another. While there are several candidate markers that deserve further investigation, there needs to be an increased focus on incorporation of biomarker assessment into large prospective clinical trials if we are to understand the clinical significance of these biomarkers. Even so, the collection of biomarker samples based on convenience leads to difficulty in interpretation of results. Ideally, the best biomarkers should be defined upfront and clinical trials of therapy designed around them in order to build on their utility.

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Footnote

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