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RESEARCH HIGHLIGHT

Predicting responses to sunitinib using single nucleotide polymorphisms: progress and recommendations for future trials

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Abstract

Targeted therapy with tyrosine kinase inhibitors has led to a substantial improvement in the standard of care for patients with advanced or metastatic clear cell renal cell carcinoma. Because the mechanism of action, metabolism and transport of tyrosine kinase inhibitors can affect outcome and toxicity, several investigators have pursued the identification of single nucleotide polymorphisms (SNPs) in genes associated with these actions. We discuss SNPs associated with outcome and toxicity following sunitinib therapy and provide recommendations for future trials to facilitate the use of SNPs in personalized therapy for this disease.

Metastatic renal cell carcinoma (RCC) is a heterogeneous disease, and the selection of treatment and the prediction of outcome are currently based mainly on tumor histology. In recent years several drugs have been approved for treatment of advanced RCC, but side effects are limiting their use. If toxic effects could be predicted then better treatment could be provided. Uncovering the genetics that underlies RCC and the pharmacogenetics that controls drug effects is crucial if treatment is to be improved.

The clear cell histological subtype of RCC accounts for more than 75% of kidney tumors and is presumed to arise from the proximal convoluted tubule of the kidney [1]. Sporadic tumors make up 75 to 85% of all clear cell RCC, and more than 75% of such sporadic tumors have been found to have defects in the von Hippel-Lindau (*VHL*) gene [1]. The VHL protein is a tumor suppressor and *VHL* mutations that inactivate suppression lead to transcription of hypoxia-inducible genes, including those encoding vascular endothelial growth factor (VEGF), platelet derived growth factor-β (PDGF-β), transforming growth factor-α and erythropoietin. The highly vascular characteristic of clear cell RCC and the discovery of a potential central role for VEGF signaling triggered the search for agents that target these pathways for the treatment of clear cell RCC.

Since December 2005, the clinical management of clear cell RCC has been boosted by the approval of several agents that target tumor cells. These include the humanized monocolonal antibody bevacizumab, which targets VEGF, the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus, and the multi-targeted tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib and pazopanib (Box 1) [1]. Despite the clinical efficacy of these agents, which have revolutionized the standard of care, toxicities such as hypertension, myelosuppression (reduction in white blood cells and platelets) and skin reactions such as the palmar plantar dysesthesia that are associated with their chronic use affect the choice of these agents for therapy. The side effects caused by TKI therapy have been attributed to their potency at inhibiting VEGF receptors (VEGFRs) and Flt-3 [2,3].

TKIs provide a promising clinical outcome and so there is a need to manage the accompanying toxicity. Substantial effort has been directed at identifying SNPs that can predict activity and/or toxicity, and a recent publication by Garcia-Donas *et al.* [4] in the *Lancet Oncology* is another step in the right direction. The authors [4] provide data demonstrating that a panel of selected SNPs can be useful in predicting the activity or toxicity that develops during sunitinib treatment. This is the first prospective study in previously untreated patients, and it evaluates various outcome measures in patients with metastatic clear cell RCC being treated with sunitinib. The study used a panel of 16 key polymorphisms in 9 genes that are linked to the mechanism of action, metabolism and transport of sunitinib to evaluate SNPs in germline DNA isolated from peripheral blood or saliva.

The prospective nature of this research is important; however, the study [4] was conducted in a practice

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Box 1 Systemic therapy for locally advanced or metastatic RCC

Multikinase inhibitors
- Sunitinib
- Pazopanib
- Sorafenib

VEGF inhibition and cytokine
- Bevacizumab and interferon-α

mTOR inhibitors
- Everolimus
- Temsirolimus

Cytokines
- IL2
- Interferon-α

Chemotherapy

setting, with no protocol guidance for investigators regarding dose levels, dose adjustments and clinical evaluations. As an example, 10% of patients received starting doses of less than the recommended standard level of 50 mg/day of sunitinib. The primary determinant of efficacy used in this work is progression-free survival (PFS); however, in an uncontrolled setting determination of PFS is sometimes problematic because of the risk of investigator and/or patient bias. In addition, no data are provided about the frequency of missed scans, which can influence PFS determination [5], and 11 of 101 (>10%) patients were eliminated from the analysis for various reasons. Therefore, the clinical trial design and data collection procedures are unclear and may represent critical issues for evaluation of the SNP data. Finally, the optimal efficacy endpoint is overall survival; use of surrogates such as PFS and/or response may be acceptable if overall survival is confounded by the study design or subsequent therapy. A limitation is that this study and others have evaluated several overlapping SNPs for response and/or toxicity following treatment with sunitinib in patients with metastatic clear cell RCC, yet there is no consensus on a set of 'predictive' SNPs. Despite these drawbacks, the authors [4] identified polymorphisms in the cytochrome P450 gene *CYP3A5*1* and *VEGFR3* that correlate with tolerability and response, respectively, to sunitinib treatment.

The strategy to evaluate germline DNA as described in this study and used by others certainly provides a convenient and reliable source of high quality DNA for SNP analysis. Thus, one would expect that, at least with enzymes involved in sunitinib metabolism, such as CYP3A5*1 (rs776746), polymorphisms in the germline DNA should provide consistent data for toxicity between studies [4,6]. The data of Garcia-Donas *et al.* [4] clearly outline a significant role for allelic genotypic differences in CYP3A5*1 (rs776746) that are correlated with dose reductions, whereas that of van der Veldt *et al.* [6] describes a significant correlation with PFS for the same polymorphism. Similarly, VEGFR3 (rs307826) had an effect on PFS in the study by Garcia-Donas *et al.* [4] but a similar association was not reported in the study by van der Veldt *et al.* [6].

As the study by Garcia-Donas *et al.* [4] exclusively evaluated untreated patients, whereas the van der Veldt *et al.* [6] study examined treatment-naïve and previously treated patients, previous treatment may be relevant in defining the role of a specific SNP. Garcia-Donas *et al.* [4] identified two VEGFR3 polymorphisms (rs307826 and rs307821) that had a significant effect on PFS. However, an obvious piece of data that is lacking in all studies evaluating SNPs in TKI-treated patients [4,6-9] is the effect of dose or of dose modifications on pharmacokinetics and circulating VEGF/VEGFR levels. Also, is there a correlation between genotype frequency for a particular SNP in germline DNA and the paired genomic tumor DNA from the same patient? The study by Kim *et al.* [9] indicated a greater than 98% correlation between the genotype for VEGF and VEGFR2 SNPs in paired germline and tumor DNA, suggesting that using germline DNA for analysis of SNPs in patients treated with TKIs could be informative.

Another important aspect is the effect of previous treatment on PFS. For example, Xu *et al.* [8] evaluated the efficacy of the TKI pazopanib in treatment-naïve and previously treated patients and identified polymorphisms in the interleukin 8 (*IL8*), hypoxia-inducible factor 1 alpha (*HIF1A*) and *VEGFA* genes that were associated with PFS or response rate. Although these data are related to treatment with pazopanib and not sunitinib, this information should be considered in the context of a patient who is refractory to sunitinib being subsequently treated with sorafenib, pazopanib or an mTOR inhibitor. Thus, delineating the predictive role of SNPs in treatment-naïve and previously treated patients could be important in defining SNPs as a biomarker on which to base the choice of drug for therapy.

A further consideration is that because germline DNA is used for analysis of SNPs, the role of the host response to the TKI or mTOR inhibitor becomes paramount, because the precise mechanism of action for anti-tumor activity of these targeted agents is yet to be defined. It would also be useful to identify a subset of SNPs from different genes, for example, those encoding VEGF and VEGFR2, associated with a signaling pathway and outcome, as described by Kim *et al.* [9] in their study evaluating metastatic clear cell RCC patients treated with sunitinib, because this could emphasize the relative significance of certain SNPs based on previous therapy and the targeted therapy of choice.

In summary, the interesting data from Garcia-Donas *et al.* [4] provide additional information on the association of SNPs with response and toxicity in sunitinib-treated patients. They also raise important considerations for trials with TKI or mTOR inhibitors, and we have four recommendations for future clinical trials. Firstly, pharmacokinetics will need to be defined to better understand the relevance to response and toxicity; secondly, the potential differences in treatment-naïve and pre-treated patients need to be included; thirdly, study design and endpoint evaluation must be prospective and include a well-designed protocol, with sufficient patient numbers, and critical evaluation of toxicity and efficacy endpoints; and finally, recommended guidelines for defining a biomarker [10] need to be considered, so that SNPs truly enter the arena of personalized targeted therapy for clear cell RCC.

Abbreviations

CYP, cytochrome P450; mTOR, mammalian target of rapamycin; PFS, progression-free survival; RCC, renal cell carcinoma; SNP, single nucleotide polymorphism; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VHL, von Hippel-Lindau.

Competing interests

RNG has previously received research funding from Bayer, Novartis and Pfizer for studies in renal cell carcinoma. RMB is a consultant and speaker for Pfizer, Genentech, Novartis and GSK, and a consultant for BMS and Argos.

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