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METASTATIC RENAL CANCER: PROGNOSTIC AND PREDICTIVE BIOMARKERS REVIEW

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Absract – *The stratification of patients with metastatic Renal Cell Carcinoma (mRCC) into risk categories is mandatory to create a prognostic scoring systems and to guide an adequate therapeutic decisions. The aim of this article is to describe the main biological and clinical factors impacting on treatment decision-making.*

INTRODUCTION

In recent years the introduction of several drugs, tyrosine kinase and anti-angiogenic inhibitors, have revolutionized the treatment of metastatic renal cell carcinoma, improving progression-free survival and overall survival. The understanding of the different molecular pathways involved in renal cell carcinoma (RCC) pathogenesis allowes the identification of several biomarkers as prognostic and predictive factors[1] in order to create a renal cancer prognostic system to guide clinical decision-making.

PROGNOSTIC BIOMARKERS

A *prognostic* biomarker is a molecule that predicts survival despite any treatment; it is indicative of the innate tumour aggressiveness[2]. We can identify clinical, genetic and tissue factors.

Clinical and serum markers

The performance status (PS), according to the Eastern Cooperative Oncology Group (ECOG) or Karnofsky, is the marker with the greatest relevance and it highlights the impact of disease on patients overall health status[3].

The first elaborated prognostic model, derived from a retrospective analysis of mRCC patients treated with Interferon (IFN), considered: the ECOG PS, the period between diagnosis and first systemic treatment, the number of metastatic sites, previous cytotoxic chemotherapies, and weight loss[4]. On the basis of these factors, the authors[5,6] stratified patients in five groups with different survival rates; then other integrated models was designed. To date, the two most widely used score systems in clinical practice and trials are the MSKCC (Memorial Sloan Kettering Cancer Center) for the metastatic setting and the UISS (University of California at Los Angeles Integrated Staging System) for resected kidney cancer without metastatic sites[7]. The MSKCC or Motzer criteria, stratifies patients according to five prognostic factors (three serum markers and two clinical markers) significantly correlated with overall survival (OS). The serum markers are: LDH greater than 1.5 times the upper limit of normal (ULN), corrected serum calcium greater than the ULN, and serum hemoglobin less than the lower limit of normal (LLN); the clinical markers are Karnofsky performance status less than 80, interval from diagnosis to treatment of less than 1 year[6,8]. Using these variables, patients are stratified in three groups (good, intermediate and poor risk) with dif-

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Table 1. MSKCC score system.

Score systems			
KARNOFSKY PS		< 80%	
Haemoglobin		< lower normal limit	
Lactate Dehydrogenase (LDH)		1.5 x upper normal limit	
Corrected Serum Calcium		> 10 mg/dl	
Period from diagnosis to treatment		< 1 year	
Prognosis	***Score***	***Median Overall Survival (months)***	***Survival at 3 years (%)***
Good	0	30	45%
Intermediate	1-2	14	17%
Poor	3-4-5	5	2%

ferent OS, ranged from 20 months (good prognosis) to 4 months (poor prognosis). Mekhail and colleagues revealed the need to add to Motzer's prognostic scoring system, the use of radiation treatment and number of metastatic sites. The introduction of these new parameters allowes a redistribution of patients, initially included in the intermediate prognosis group, to the group with a poor prognosis[9]. Another prognostic model, obtained from patients treated with VEGF-targeted therapy, is the International mRCC Database Consortium (IMRDC) or Heng's model. This model was derived from a retrospective analysis of 645 patients with mRCC treated with sunitinib, sorafenib or bevacizumab plus interferon. Patients who received prior immunotherapy were also included in the analysis. The authors identified six clinical parameters to stratify patients into good, intermediate, and poor prognosis group. Additional independent adverse prognostic factors validated in this model were absolute neutrophil count higher than ULN and platelets higher than ULN[10].

Tissue factors

Several prognostic factors have been studied to predict RCC recurrence including tumour stage, nuclear Fuhrman grade, histology, presence of a sarcomatoid component or tumor necrosis, microvascular invasion and involvement of the collector system. The nuclear Fuhrman grade remains the only tissue factor considered an independent prognostic indicator for RCC[11,12]. A pathological review of RCC revealed that more than half of the analysed samples, showed deviations from classical clear cell features, suggesting that such tumours need a different classification[13,14]. Using gene expression signatures, it is possible to discern, with more than 90% of accuracy, between clear cell, papillary and chromophobe RCCs as well as benign oncocytomas[15]. Such profiling could be an important tool in the clinical practice, if validated, for subtyping unclassifiable tumours or in cases with unclear diagnosis (for example, eosinophilic tumours). The main subtype of RCC is the clear cell one, followed by papillary type I and II, and by the chromophobe type. Many studies confirmed the prognostic value of histology and identified in clear cell carcinoma the most aggressive subtype. On the other hand, in most of the multivariate models the prognostic significance of histology lost importance in favour of tumour stage and grade[16].

Table 1. Cleveland Clinic score system.

KARNOFSKY PS	< 80%
Haemoglobin	< lower normal limit
Lactate Dehydrogenase (LDH)	1.5 x upper normal limit
Corrected Serum Calcium	> 10 mg/dl
Period from diagnosis to treatment	< 1 year
N° metastatic sites	> 1
Previous Radiotherapy	YES

PREDICTIVE BIOMARKERS

A *predictive* biomarker is a molecule that predicts therapeutic efficacy that usually implicates an interaction between the molecule and the therapy and affects patient's outcome. We can identify, within this group, clinical, genetic and tissue markers.

Clinical factors

The onset of targeted therapy era has completely changed the scenario of mRCC treatment. Most agents inhibit cellular signalling by targeting multiple receptor tyrosine kinases (RTKs) with a block

of tyrosine kinase domain (TKI) of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptors (PDGFRs) and other receptors such as KIT, RET, flt3, that have an important role in tumour angiogenesis and tumour cell proliferation[17]; the simultaneous inhibition of these targets leads to reduced tumour vascularisation, cancer cell death and tumour shrinkage. These drugs include sunitinib, sorafenib, pazopanib, axitinib. Another kind of inhibition is the one carried out by bevacizumab, a humanized monoclonal antibody that binds vascular endothelial growth factor A (VEGF-A). The mammalian target of rapamycin (mTOR) inhibitors, temsirolimus and everolimus, are also approved in this setting. The analysis of molecular markers, as predictive factors, may lead to a rational selection of patients able to benefit from a kind of therapy rather than another one.

Treatment selection is currently based on clinical and serum parameters according to selection criteria for prognostic risk developed by the Memorial Sloan-Kettering Cancer Center and based primarily on PFS and OS data reported in phase III clinical trial[18].

The different selectivity and pharmacodynamic mechanism of these agents explain the different side effects reported by each drug. Their occurrence are due to the inhibition of target receptors, such as VEGFR (on-target effects) and to the interactions with other tyrosine kinase receptors (off-target interactions)[19]. Many studies revealed that the development of some drug-induced adverse events could be considered as a surrogate marker of its clinical activity with predictive value for treatment outcome. The side effect, in this context, would be related to a major exposure to the drug and therefore it represents a marker for its increased efficacy. On the opposite, the absence of side effects would be related to sub-therapeutic levels of circulating drug leading to less therapeutic effects. Specific adverse events, now under validation, are hypertension, hypothyroidism, hand-foot syndrome and fatigue[20].

Hypertension (HTN) is an on-target effect of the vascular endothelial growth factor pathway inhibitors and the most common adverse event in patients with solid tumours treated with these drugs. The pathological mechanism by which VEGF-pathway inhibition leads to an increase in blood pressure (BP) is unclear but a generalised dysfunction of microcirculation seems to be the primary cause; other pathways implicated are activation of the endothelin-1 system, suppression of the renin-angiotensin system, inhibition of endothelial nitric oxide synthase and increased vascular stiffness[21-23]. Many studies evaluated the association between sunitinib-induced HTN and its antitumor efficacy. Across these studies, the incidence of all-grade and grade 3/4 hypertension varied widely, probably due both to the different adopted protocols for measuring blood pressure, that to differences in the study patient populations[24-29]. A retrospective review from three multi-centric clinical trials[17,18], found a significant positive association between sunitinib-induced hypertension and PFS, OS and objective response rate (ORR)[30]. Hypertension was associated with a fourfold improvement in PFS and OS and a sixfold improvement in ORR in patients treated with sunitinib.

The use of antihypertensive medications at the baseline was associated with statistically significant greater OS; in fact, patients with normal blood vessel morphology may be particularly sensitive to VEGF blockade[30].

Hypothyroidism is another known side effect of treatment with VEGFR TKIs and is usually mild or moderate; it is recognised in about 14% of patients treated with these agents[31,32]. The mechanism leading to VEGFR TKIs related hypothyroidism is not fully understood. Probably it is associated with a destructive thyroiditis resulting in follicular cell apoptosis[31], endothelial dysfunction[33,34], inhibition of iodine uptake[35,36] and reduced synthesis of thyroid hormone[33]. Hypothyroidism treatment consists of thyroid hormone replacement therapy to allow normalisation of thyroid-stimulating hormone (TSH) levels and resolution of symptoms. Wolter et al.[37] evaluated a possible association between sunitinib outcome and thyroid dysfunction in 40 patients with advanced RCC. This study recorded a higher median PFS (10.3 vs 3.6 months) and median OS (18.2 vs 6.6 months) in patients with the appearance of thyroid dysfunction versus normal thyroid function, respectively. The development of subclinical hypothyroidism within the first 2 months of treatment was an independent predictor of survival[38,39].

A prospective study of 111 patients with mRCC treated with sunitinib did not find any association between abnormal thyroid function and PFS[40] without significant difference between patients with and without thyroid dysfunction (18.9 versus 15.9 months, respectively). In this study, patients were treated with hormone replacement therapy.

Hand-foot syndrome (HFS) of any grade is reported in up to 51% of patients treated with TKIs with only 9% of Grade 3/4. Its pathogenesis is related to the blockade of VEGFR and PDGFR, resulting in dermal endothelial cell apoptosis. Another possible cause can be c-KIT inhibition. TKIs may have a direct toxic effect when secreted into the eccrine glands of the skin that are rich in c-KIT[41-43]. A retrospective analysis found that HFS development was related to a better clinical out-

come with longer OS, PFS and better ORR[44]. On this basis, HFS remains a significant independent predictor of PFS and OS[45].

Fatigue is a common side effect reported in patients receiving a TKIs therapy. Its pathogenesis is complex and may be directly related to the disease or to the use of co-medications, anaemia or hypothyroidism. It was reported in 19%-54% of patients with mRCC treated with target therapy[46]. Several studies investigated the role of fatigue as a predictive factor and it was showed that patients who developed fatigue or asthenia had statistically significantly better clinical outcomes in terms of PFS and OS[45,47]. After a multivariate analysis, fatigue or asthenia remained independent predictors for outcomes and could be related to hypopituitarism[48].

Pneumonitis are the most serious side effect of mTOR inhibitors and are probably due to a hypersensitivity response[49,50]. This effect occurs in 2%-29% of patients with mRCC treated with temsirolimus. This range reflects the different diagnostic system used in each study (according to symptoms, it is diagnosed in 2-5% of patients, according to radiology it is diagnosed in 29% of patients)[51-53]. Similar findings have been reported with everolimus, the range was 6% to 13% in clinical trials [54,55], and 54% in a radiographic review[6]. Data suggest that the incidence of pneumonitis may be higher in Asian patients than other ethnicities[57]. Its development may be a marker of therapeutic benefit in patients treated with mTOR inhibitors. In a review of clinical data among patients with pneumonitis, 86% achieved stable disease and 14% had progressive disease. Of those without pneumonitis, 44% had stable disease and 56% had progressive disease.

Other potential biomarkers

Metabolic disorders such as increase in serum cholesterol, triglyceride and glucose levels, that commonly occur with the use of mTOR inhibitors, may be considered as serum predictor factors and the association of their changes with temsirolimus and everolimus efficacy, is under investigation. Preliminary studies suggested that an increase in cholesterol levels, and not glucose or triglycerides, was associated with longer OS and PFS, while other studies did not confirm this predictive role[58].

To date, HTN represents the most promising and well-studied predictive clinical factors in mRCC treated with VEGF inhibitors. However, further investigations are required to validate the association between the development of adverse effects and clinical outcome, considering the possible bias related to its pharmacological therapeutic management.

Genetic factors

Many genetic biomarkers have been studied, but none of them have been evaluated in randomized clinical trials[59].

The expression of some genes and the presence or absence of single nucleotide polymorphisms (SNPs) have been associated with a differential response to targeted agents. Some studies suggest that SNPs in VEGFR3, CYP3A5*1, IL8, FGFR2, NR112 and ABCB1 may predict efficacy and tolerability. However there are currently insufficient prospective data to support the use of any molecular/genetic biomarkers in the clinical practice and we need appropriate trials for their validation.

Some of the mainly studied genetic markers in RCC include:

- Von Hippel-Lindau tumour suppressor mutations
- PBRM 1
- BAP 1
- VEGF single nucleotide polymorphisms and pathway markers

More than 90% of sporadic clear cell renal cell carcinomas (ccRCC) present *a loss of function* of VHL, a tumour suppressor gene located on chromosome 3p. The VHL gene is often inactivated (by mutation or promoter hyper-methylation) in renal cell carcinoma but its correlation with therapeutic outcome is unclear. Choueiri TK et al[60], evaluated patients with mRCC who received VEGFR inhibitors with a stratification based on patients characteristics, VHL gene status and clinical outcome. The primary endpoint was the response rate correlated to VHL inactivation; PFS and OS were secondary endpoint. Patients with VHL inactivation had a response rate of 41% vs. 31% for those with wild-type VHL ($p = 0.34$). Patients, with loss of function mutations (frameshift, nonsense and splice and in-frame deletions/insertions), had 52% response rate vs. 31% with wild-type VHL. The presence of a loss of function mutations remained an independent prognostic factor with improved response rate but without PFS and OS differences.

The SW1/SNF chromatin remodelling complex gene polybromo1 (PBRM1, also known as BAF180) is a tumour suppressor gene implicated in ccRCC development and its mutations are the second most frequent event in ccRCC, ranging from 30-50%[61-63].

PBRM1 participates in several cellular processes such as gene transcription, DNA repair and cell proliferation[64] and its mutations are an early event in metastatic ccRCC development[65-66].

Mutations of PBRM1 are frequently associated with a small (< 4 cm) but highly invasive kidney tumours.

Mutations of the BRCA1 associated protein-1 (BAP1), an ubiquitin carboxyl-terminal hydrolase, are strongly associated with adverse tumour features (e.g., higher nuclear grade, confirmed by Pena-Llopis et al) and worse cancer-related OS. Inactivating mutations occur in 15% of ccRCCs.

Mutations in PBRM1 and BAP1 are generally mutually exclusive. The median OS in the cohort with BAP1-mutant tumours was significantly shorter (4.6 years; 95% CI 2.1-7.2), than in patients with PBRM1-mutant tumours (10.6 years; CI 9.8-11.5), corresponding to a HR of 2.7 (95% CI 0.99-7.6, $p = 0.044$).

Patients with mutations in both BAP1 and PBRM1 have a worst overall survival. These findings allow identifying two mutation that define distinct subtypes of clear-cell renal-cell carcinoma with different clinical outcomes: 1) high-risk BAP1-mutant group 2) favourable PBRM1-mutant group[67].

BAP1-deficient tumours, unlike PBRM1 mutation, are characterized by highly grade. Although these findings need to be validated by studies with longer follow up. The genetic status of BAP1 is likely to be used in risk stratification of patients who present with small ccRCC.

Other genetic sites evaluated such as SET domain containing protein 2 and Jumonji AT-rich interactive domain 1C, have also been studied although with a lower frequency (3%)[67].

A promising method to sub-classify ccRCC is the use of gene expression microarrays, in order to provide prognostic information, useful in the daily clinical practice. To date, studies using these tools have a small sample size with a limited number of analysed genes and not yet validated.

Recent data of large genome-wide association study showed that some SNPs – Single Nucleotide Polymorphisms – might increase the risk of developing RCC[68-70].

Germ-line genetic variations, in addition to somatic mutations within tumours, may also help to explain the differences in response and toxicity to anticancer agents.

Some studies demonstrated that the response to TKI therapy can be affected by the presence of some SNPs. In a large study of 397 patients it was evaluated the association between pazopanib treatment and 27 polymorphisms amongst 13 genes regulating angiogenesis (VEGFA/IL-8/fibroblast growth factor 2), metabolism (cytochrome P450 (CYP) 3A4/5) and transport (ATP-binding cassette (ABC) B1). Two IL-8 polymorphisms, linked to its increased gene expression, were associated with a significantly shorter median PFS (27 weeks) versus those carrying the wild-type genotype (48 weeks)[71].

IL-8 has recently been identified as a potential driver of resistance to TKIs[72].

A second prospective study, examined response and toxicity to sunitinib in patients with ccRCC. Sixteen polymorphisms were examined in nine genes. Two VEGFR3 missense polymorphisms were associated with reduced PFS and a variant of CYP3A5*1 was associated with increased toxicity on multivariate analysis[73]. In a retrospective study of 136 patients with metastatic ccRCC treated with sunitinib, 30 SNPs in 11 genes were examined and correlated with PFS. Survival was significantly improved in relation to SNPs in CYP3A5, ligand-activated nuclear receptor NR1I3 and ABCB1, but not in VEGFR3[74].

Other important genetic predictors of treatment response seem to be VEGF SNPs. These biomarkers have been associated with differences in OS between patients treated with sunitinib with and without VEGF 936 C/C and VEGFR2 889 G/G alleles. The frequency of the reported SNPs is typically low, so further validation studies are necessary. Furthermore, these results need to be confirmed in populations of different ethnicities.

Many issues relating to the success of individualised cancer therapies come from the increasing knowledge that individual tumours are themselves highly heterogeneous[75]. Recent studies showed that the majority of mutations were not present homogeneously throughout the tumor and would diagnose only a minority of genetic aberrations. Furthermore, different areas of the same tumour presented a variety of favourable or unfavourable prognostic profiles[76], suggesting a diversity among biologically relevant mutations.

This heterogeneity is common in all cancer types and potentially carries significant implications for successful biomarkers validation and for delivery of personalized medicine.

An additional complication is that the signature of the primary tumour may not necessarily reflect that of the metastatic sites[77].

The recent genome mapping has identified 259 genes that could be useful for predicting survival in ccRCC regardless of the traditional clinical prognostic factors, even if their validation is still far from being confirmed.

Also some proteins have proven to be important for tumorigenesis and tumour progression. We can distinguish between proteins expressed by the tumour and detectable by immune-histochemical investigations of the surgical samples and proteins secreted by the tumour in the blood and detectable by analysis of the serum of patients during treatment.

Among these the most studied biomarkers are:

- VEGF - vascular endothelial growth factor
- CAIX - carbonic anhydrase IX
- CXCR4

- HIF-1α/HIF-2α-hypoxia inducible factor
- Phospho-S6
- PD-1L

Some studies identified sVEGFr-3 and VEGF-C low baseline levels as predictors of longer PFS in sunitinib treated patients.

Low as well as high baseline levels of VEGF predict longer PFS with sorafenib. Rini et al[78] have recently published the results of an expression analysis of the plasma levels of VEGF and VEGFR in patients receiving sunitinib. In a population of 63 patients evaluated, the pattern of circulating levels of VEGF, VEGFR-2 and VEGFR-3 during treatment correlated significantly with ORR.

Other studies investigated the role of tumour carbonic anhydrase IX (CAIX) expression to predict the outcome in patients with mRCC treated with VEGF inhibitors. The endpoint was the analysis of the interaction between treatment with sorafenib or sunitinib and CAIX status and its impact on tumour shrinkage. Tumour response to sunitinib or sorafenib according to CAIX status was heterogeneous without prognostic value in this setting of patients. It might be, instead, a predictive biomarker for response to sorafenib treatment. However, patients with a higher clear-cell component in their tumours were likely to have a major clinical benefit from VEGF-targeted therapy[79].

Almost 30% of the sunitinib-treated patients for metastatic renal carcinoma (mRCC) do not receive a clinical benefit. Evidences demonstrated a cross talk between the VEGF and CXCR4 pathways and hypothesized that CXCR4 expression in primary renal cancer could predict sunitinib responsiveness.

D'Alterio et al[80] included sixty-two mRCC patients receiving sunitinib as first-line and evaluated the CXCR4 expression through immunohistochemistry (IHC). Correlations between CXCR4 expression, baseline patients and tumour characteristics were studied. It was detected a correlation between high CXCR4 expression and poor response to sunitinib in metastatic renal cancer. These findings, together with the ones shown by Guo J et al[81] allow us to draw these conclusions:

High CXCR4 expression correlates with poor response to sunitinib

Patients treated with sorafenib with low or no CXCR4 expression have higher PFS (20.0+5.9 mo) than those with intermediate or high CXCR4 (6.0+0.8 mo) (pv = .038)

There is no correlation between low or no CXCR4 expression and PFS in patients treated with sunitinib.

Other scientific evidences showed that patients with higher levels of HIF-1α or HIF-2α were more likely to achieve complete response (CR) or partial response (PR) with sunitinib therapy.io

Patients, with high Phospho-S6 levels versus those with intermediate or low S6 expression, showed a median OS of 17.3 versus 9.1 months when treated with temsirolimus[82].

RCC is a heterogeneous tumour that involves several molecular pathways in its development so it is difficult to predict individual response to treatment and clinical benefit. The main difficulty for the definition of specific and generalized tumour characteristics concerns the intra-tumour heterogeneity and the lack of tumour specimens for translational research.

Our hope is to be able to use such biomarkers for early identification of responding patients and to better select the best therapy in each moment of disease development.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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