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Anti-Tumour Treatment

The prospect of precision therapy for renal cell carcinoma

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ABSTRACT

The therapeutic landscape of renal cell carcinoma (RCC) has greatly expanded in the last decade. From being a malignancy orphan of effective therapies, kidney cancer has become today a tumor with several treatment options. Renal cell carcinoma (RCC) is a metabolic disease, being characterized by the dysregulation of metabolic pathways involved in oxygen sensing (VHL/HIF pathway alterations and the subsequent up-regulation of HIF-responsive genes such as VEGF, PDGF, EGF, and glucose transporters GLUT1 and GLUT4, which justify the RCC reliance on aerobic glycolysis), energy sensing (fumarate hydratase-deficient, succinate dehydrogenase-deficient RCC, mutations of HGF/MET pathway resulting in the metabolic Warburg shift marked by RCC increased dependence on aerobic glycolysis and the pentose phosphate shunt, augmented lipogenesis, and reduced AMPK and Krebs cycle activity) and/or nutrient sensing cascade (deregulation of AMPK-TSC1/2-mTOR and PI3 K-Akt-mTOR pathways).

In this complex scenario it is important to find prognostic and predictive factors that can help in decision making in the treatment of mRCC.

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Introduction

The therapeutic landscape of renal cell carcinoma (RCC) has greatly expanded in the last decade. From being a malignancy orphan of effective therapies, kidney cancer has become today a tumor with several treatment options.

Angiogenesis – a dynamic process required to sustain tumor cells growth and metastatic spread, mediated by multiple pro-angiogenic factors (of which VEGF is certainly the most important) and influenced by the tumor microenvironment – is the hallmark of ccRCC. Therefore, angiogenesis represents one of the key target for therapy, explaining the antitumor activity of anti-VEGF targeted agents (VEGFR tyrosine-kinase inhibitors – sunitinib [1], pazopanib [2,3], axitinib [4], and sorafenib [5] –, and the anti-VEGF monoclonal antibody – bevacizumab [6]). In addiction, tumor growth relies on the mTOR pathway hyperactivation, justifying the efficacy of mTOR-inhibitors (temsirolimus [7] and everolimus [8]). More recently, it has awakened an old interest in the role of the immune system in controlling RCC cancerogenesis and progression. The immune checkpoint inhibitor targeting the PD-1/PD-L1 axis – nivolumab –, by stimulating the hosts' antitumor immunity, represents one of the main oncological breakthroughs, causing impressive long-lasting responses and significantly prolonging overall survival (OS) of RCC patients [9]. Choosing from the available therapies maximizing the efficacy and minimizing the toxicity is the future challenge. Identifying predictors of response leading to a personalized therapy represents the main goal of cancer research. What drives decision making in the treatment of RCC patients?

Tumor histology

Clinicians are used to classify RCC based on tumor histology, distinguishing the most frequent clear cell RCC type (accounting singly for about 70–85% of renal tumors) from the other RCC sub-

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types, which are simplistically grouped as non-clear cell RCC (nccRCC).

Actually, the bulk container of nccRCC tumors includes multiple different malignancies profoundly diverse in terms of morphological and immunohistochemical features, molecular genetic profile, clinical behavior and prognosis [10–12].

Current treatment recommendations for nccRCC patients are borrowed from evidence available for ccRCC, lacking robust direct evidence of effective therapies for nccRCC patients that are generally excluded or underrepresented in pivotal clinical trials testing the novel compounds [13]. To date, the two most recent and large prospective studies (ESPN and ASPEN) conducted in patients with non-clear-cell RCC compared the use of sunitinib to everolimus, failed in demonstrating the superiority of the mTOR-inhibitor over the VEGFR-targeted agent [14,15]. Both trials demonstrated a prolonged PFS for first-line sunitinib (mPFS 8.3 vs 5.6 months and 6.1 vs 4.1 months in the ASPN and ESPN trials respectively), with everolimus therapy providing benefit only in certain subgroups of patients (poor risk and chromophobe subtypes), but this evidence is not sufficient to recommend everolimus as preferable option in poor risk and chromofobe subtypes. It is important to point out that, regardless of the type of therapy (sunitinib or everolimus), non-clear cell RCC histotypes display shorter PFS times and lower RRs than the clear cell RCC counterpart, reinforcing the acknowledge worse outcome of nccRCC patients treated with VEGF- and mTOR-targeted therapies compared to ccRCC patients (mOS 22.3 vs 12.8 months; $p < .0001$) [16].

Clinical prognostic factors

To date, the only validated systems for prognostically stratifying patients with metastatic renal cell carcinoma rely on the evaluation of clinical factors, since no molecular biomarkers with a prognostic or predictive value have been identified so far.

The Memorial Sloan-Kettering Cancer Center (MSKCC) risk model categorizes patients with metastatic RCC treated with interferon-alfa as first-line systemic therapy into three risk groups based on five pretreatment clinical factors prognostic of short survival (Karnofsky performance status <80%, serum lactate dehydrogenase >1.5 times upper limit of normal [ULN], low serum hemoglobin, "corrected" serum calcium >10 mg/dL, and time from initial RCC diagnosis to start of systemic therapy of less than one year) [17,18]. The median survival times range from approximately 5 months for poor risk patients (with 3 or more risk factors) to more than 29 months for patients with a good prognosis (with no risk factors) [18]. An independent group at the Cleveland clinic subsequently validated the MSKCC criteria, by using a data set of 353 patients enrolled on clinical trials involving immunotherapy [19]. Of note, the MSKCC prognostic risk model was developed in the era of immunotherapy, and limited to patients eligible for participation in immunotherapy clinical trials.

The approval of VEGFR-targeted agents had subsequently required a novel prognostic system capable of better stratifying patients in clinical trials, providing clinical information to patients receiving therapy, and helping risk-directed treatment selection in daily clinical practice in the era of targeted therapy. Heng et al. identified a prognostic model (the IMDC risk score) composed of two clinical (Karnofsky performance status less than 80%, time from diagnosis to treatment of less than one year) and four laboratory values (hemoglobin less than lower limit of normal, corrected calcium greater than ULN, neutrophils greater than ULN, and platelets greater than ULN) able to stratify patients into favorable (43.2 mOS months), intermediate (22.5 mOS months), and poor prognosis groups (7.8 mOS months) [20,21]. Of note, the IMDC prognostic model reliably predicts OS not only in ccRCC patients, but also in non-clear cell RCC histology [16] (Table 1).

Table 1
Heng and MSKCC prognostic factors.

Modified MSKCC prognostic factors	Heng prognostic factors
• LDH > 1.5 × upper limit of normal • Corrected Calcium > 10 mg/dL • Time from diagnosis to first treatment < 1 year • Karnofsky performance status 60–70 • Multiple organ sites metatsasis	• Hemoglobin less than lower limit of normal • Corrected calcium above the upper limit of normal • Time from diagnosis to treatment < 1 year • Karnovsky performance status < 80% • Platelets greater than the upper limit of normal • Neutrophils greater than the upper limit of normal

LDH: lactate dehydrogenase; MSKCC: Memorial Sloan Kettering Cancer Center.

Molecular-based classification of renal cell carcinoma

Efforts are directed at delineating signaling pathways underlying clear cell and non-clear cell RCC carcinogenesis, possibly identifying driven-mutations as potential targets for therapy.

The comprehensive molecular characterization of clear cell RCC conducted by the cancer genome Atlas research network represented a fundamental step towards the deep understanding of RCC carcinogenesis [22].

In particular, the whole exome sequencing identified 19 significantly mutated genes, with VHL, PBRM1, SETD2, KDM5C, PTEN, BAP1, MTOR and TP53 representing the 8 most extreme members.

As regard the DNA methylation profiles, epigenetic silencing involved VHL in 7% of cases and the tumor suppressor UQCRH gene in 36%. Moreover, mutations in the specific epigenetic modifier SETD2 (H3K36 methyltransferase) determined widespread DNA hypomethylation.

Unsupervised clustering methods identified four stable subsets in both mRNA (m1–m4) and miRNA (mi1–mi4) expression datasets: the m1-subtype with PBRM1 mutations, the m3-subtype with deletion of CDKN2A and mutations of PTEN, and the m4-subtype with mutations of BAP1 and mTOR.

Integrative pathway analysis supported the importance of the VHL/HIF pathway, the key role of PI3K/AKT in tumor progression, and the role of chromatin modifier genes in renal tumorigenesis. In particular, alterations in SWI/SNF chromatin remodeling complex (PBRM1, ARID1A, SMARCA4) could have far-reaching effects on other pathways. Chromosome 3p-encoded chromatin remodeling tumor suppressor genes, SETD2, PBRM1 and BAP1 are frequently mutated in ccRCC (respectively in about 15%, 40%, and 15% of cases) [22,23]. Of note, BAP1 and PBRM1 mutations, which are mutually exclusive [24], identify new distinctive classes of RCC with different clinical behavior: a poor-prognosis BAP1-mutant group and a favorable PBRM1-mutant group [25].

Finally, the ATLAS ccRCC characterization identified a specific subtype of ccRCC, with aggressive behavior and poor prognosis, marked by a metabolic shift (Warburg-effect – tumor dependence on aerobic glycolysis) characterized by increased dependence on the pentose phosphate shunt, increased glutamine transport, decreased AMPK and Krebs cycle activity, and increased fatty acid production [22,26]. Dysregulation of cellular metabolic pathways involved in oxygen, energy and/or nutrient sensing is a peculiar feature of ccRCC, offering new opportunities for disease treatment.

A substantial contribution in understanding the genetic basis of nccRCC comes from familiar studies of hereditary tumors, marked by germline mutations in specific oncogenes or onco-suppressors. These hereditary cancer syndromes are paradigmatic circumstances in which a specific gene mutation, pathognomonic of a definite histotype, can translate into a definite therapeutic target:

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