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Successes and Limitations of Targeted Therapies in Renal Cell Carcinoma

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Abstract

Until recently, the standard treatment for metastatic renal cell carcinoma (RCC) was nonspecific immunotherapy based on interleukin-2 or interferon-α. This was associated with a modest survival benefit and with significant clinical toxicities. The understanding of numerous molecular pathways in RCC, including HIF, VEGF, mTOR, and the consecutive use of targeted therapies since the beginning of 2005 have significantly improved outcomes for patients with metastatic RCC with an overall survival greater than 2 years. At present, at least 7 targeted agents are approved for first and consecutive lines of treatment of clear cell metastatic RCC. Long-term benefit and extended survival may be achieved through the optimal use of targeted therapies: optimal dosing, adverse event management and treatment duration and compliance. Advances in the finding of prognostic factors highlight the potential for personalizing treatment for patients with metastatic RCC. Data regarding the best sequencing of targeted therapies, predictive biomarkers, best timing of surgery, patient risk profiles, understanding of resistance mechanisms and safety of targeted therapies are growing and will provide a further step ahead in the management of advanced RCC. In parallel, a new class of therapeutics is emerging in RCC: immunotherapy; in particular check-point blockade antibodies are showing very promising results.

Introduction

Epidemiology

Renal cell carcinoma (RCC) represents the sixth most frequent cancer in developed countries [1]; there are about 209,000 new cases of RCC and more than 102,000 deaths worldwide. This corresponds to about 2–3% of all malignant tumors in the adult [2].

Table 1. Genetic abnormalities, oncogenic pathways and prevalence associated with sporadic RCC

RCC subtype	Genetic abnormality	Oncogenic pathway	Prevalence (sporadic RCC)	Hereditary predisposition syndrome
ccRCC	VHL	VHL/HIF/VEGF PI3K/AKT/mTOR	70–85%	Von Hippel-Lindau disease
Papillary type 1 RCC	cMET	cMET/RAF/MEK/ERK	10–15% → 60–75% type 1 → 40% type 2	Hereditary papillary RCC
Papillary type 2 RCC	fumarate hydratase	VHL/HIF/VEGF PI3K/AKT/mTOR		Hereditary leiomyomatosis and RCC
Chromophobe RCC	BHD1	cKIT/RAF/MEK/ERK	<10%	Birt-Hogg-Dubé syndrome
Collecting duct RCC (Bellini tumor)			<1%	
Translocation RCC	Xp11.2–TFE3 translocation	cMET/RAF/MEK/ERK	rare, children and young adults	

On average, metastatic dissemination is seen in 30% of new cases [3] and about 40% of patients relapse locally after nephrectomy [4]. The incidence of RCC has been rising over the last decades, most likely due to improved imaging leading to earlier diagnosis of small tumors [5]. The mortality, however, has not changed significantly since 2005.

Risk Factors

Classic risk factors are tobacco and arterial hypertension. Obesity and chronic renal insufficiency (in particular in the papillary subtype) might also be contributing factors [2]. Two to 4% of RCC are attributed to hereditary syndromes which most of the time are transmitted in an autosomic dominant manner. The most frequent syndrome is the Von Hippel-Lindau disease, which is linked to the tumor suppressor gene VHL, and in patients with this syndrome clear cell RCC (ccRCC) is the principle cause of death [6].

Histology

There are three frequent histological subtypes and others which are much rarer. The subtypes are not only characterized by their anatomical pathologic features, but also specific oncogenic properties (table 1). ccRCC is the most common type representing 70–85% followed by papillary RCC, which represents 10–15%. The chromophobe type represents less than 10%, while collecting duct RCC (Bellini tumor) represents

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less than 1% of all RCC. Further divisions can be made: the papillary type has been divided into type 1 and type 2, and this subdivision has been supported by genetic mutations. This translates also into clinical behavior where the papillary subtype 2 is generally more aggressive [2].

Prognosis before the Introduction of Targeted Agents

Before the arrival of the 2 first targeted agents approved for RCC in 2007 [7, 8], RCC was considered highly resistant to medical treatments. The overall survival of the metastatic cases was 10–20% at 5 years. Only passive immune therapies with interferon-α (IFNα) or interleukin-2 (IL-2) had shown a low proportion of objective responses [9, 10]. Long-term remissions were rare, and only occasionally achieved with high-dose IL-2. High-dose IL-2 has been offered only in few centers, with a treatment-related mortality of about 3%.

Clear Cell Renal Carcinoma Biology

ccRCC is dependent on two main oncogenic pathways, the VHL/HIF/VEGF pathway and the PI3K/AKT/mTOR pathway (fig. 1).

The VHL/HIF/VEGF Pathway

The tumor suppressor gene VHL is an early and central element of ccRCC carcinogenesis [11]. Inactivation by mutation, deletion or hypermethylation of his promoter is detected in 60% of sporadic ccRCCs [12]. The VHL mutation is closely related to the hypoxia-inducible factor (HIF-α). In the normal cell with an active VHL gene, HIF-α is regulated by hydroxylation in the presence of oxygen. In hypoxic conditions, HIF is a transcription factor that activates genes that encode for proteins such as VEGF, PDGF and TGF-α, GLUT1 and EPO, which all act as angiogenic factors [13]. Therefore, the inactivation of VHL implies overexpression of these new angiogenic factors. Given the fact that VEGF as well as PDGF are central mechanisms in the development and progression of RCC [14], these pathways seemed appropriate as targets for new therapeutic strategies [15].

The PI3K/AKT/mTOR Pathway

This pathway is downstream to many growth factor receptors such as VEGF, PDGF and others. If the receptors are activated, the first mediator consecutively activated is PI3K, which then activates AKT, while PTEN represents an inhibitor of AKT. AKT itself is an activator of mTOR which acts on the transduction of multiple mRNAs, particularly on those interfering with cell survival. mTOR induces the expression of HIF-α which then leads to the induction of growth factors such as VEGF, PDGF,

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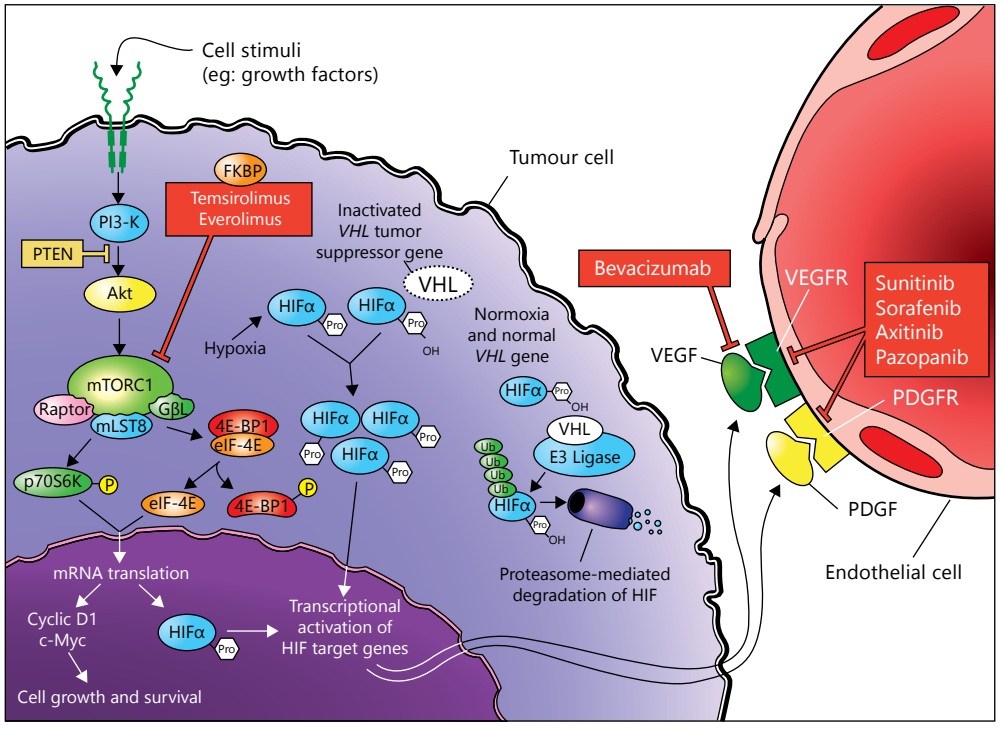

Fig. 1. Biological pathways targeted for therapy in RCC. From Vasudev et al. [64].

TGF-α, EGF, and others. This leads to enhance survival of cancer cells as well as angiogenesis [16]. The PI3K pathway is frequently overactivated in ccRCC [17]. Therefore, mTOR-inhibitors exerts their therapeutic activity by reducing VEGF signaling and decreasing survival signals.

Success of Targeted Therapies in a Clear Cell Renal Carcinoma

Prognostic Factors

Before discussing the systemic treatment options of RCC, the prognostic factors need to be understood as they have guided the recent drug development.

Retrospective data of the cytokine era [18] were used to generate prognostic factors for metastatic RCC also known as the MSKCC criteria or Motzer criteria. Unfavorable prognostic factors include high LDH, low Karnofsky performance status, low hemoglobin levels, high corrected calcium levels as well as the time from initial diagnosis to start of systemic treatment (> or < than one year). Patients were divided into groups of low, intermediate or high risk. The risk group was correlated with a medium life expectancy of 30, 14 or 5 months respectively [19].

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Table 2. Heng criteria and prognosis according to Heng criteria

a Heng criteria

Prognostic risk factor	Cutoff value
Karnovsky performance status	<80%
Hemoglobin	<N
Time from diagnosis to treatment	<1 year
Corrected calcium	>N
Platelet count	>N
Neutrophil count	>N

b Prognosis according to Heng criteria

Number of risk factors	Risk group	Median OS, months	Two-year OS, %
0	Favorable	43.2	75
1–2	Intermediate	22.5	53
3–6	Poor	7.8	7

OS = Overall survival.

An updated prognostic model has been presented by Heng et al. [20] based on patients treated with VEGF-targeted therapy. This analysis confirmed the previously reported MSKCC criteria, adding high neutrophil and platelet counts as additional unfavorable prognostic factors (table 2).

Systemic Therapy

First-Line Treatment

For patients with a good or intermediate risk and metastatic RCC with clear cell component, the treatment options today are sunitinib [7, 21], sorafenib [8, 22], bevacizumab combined with IFNα [23–26] as well as pazopanib [27, 28]. The choice between these agents is not always based on objective criteria but might be influenced by the approval of national health authorities or by a physician or patient's preference (oral vs. i.v.). The main results of the pivotal phase III trials are summarized in table 3. When these agents became first available in 2005, they revolutionized the treatment of mRCC. Sunitinib, until recently the most frequently used first-line treatment, was compared against IFNα in a study including 750 patients [7, 21]. The median progression-free survival (PFS) and median overall survival were respectively longer in the sunitinib group than in the IFNα group (11.0 vs. 5.0 months, $p < 0.001$, and 26.4 vs. 21.8, $p =$

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