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Anti-Tumour Treatment

Systemic treatment of renal cell cancer: A comprehensive review

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ABSTRACT

Kidney cancer represents about 5% of all new cancer diagnoses. The most common form of kidney cancer arises from renal epithelium, named renal cell carcinoma (RCC). This entity comprises different histological and molecular subtypes. Unraveling the molecular biology and cytogenetic of RCC has enabled the development of several targeted agents that have improved treatment outcomes of these patients. This article reviews all the agents currently approved for the treatment of RCC, and discuss upcoming molecules. Mechanism of action, preclinical and clinical development and ongoing trials, are presented for each agent, providing a broad vision of the current state of targeted therapy in RCC and possible future developments.

Introduction

Each year, around 64.000 and 115.000 patients are diagnosed with kidney cancer in the United States (US) and in Europe, respectively. This disease represents about 5% of all new cancer diagnosis and leads nearly to 15.000 and 49.000 deaths yearly in US and in Europe, respectively [1]. The most common form of kidney cancer arises from renal epithelium and is named renal cell carcinoma (RCC). Recently, the pathology classification of tumors of the kidney has been updated. The most frequent RCC subtypes include clear cell, papillary [types I and II] and chromophobe tumors [2]. Around 25–30% of RCC patients are diagnosed at a locally advanced or metastatic stage. An additional third of the RCCs will recur after a successful treatment for a localized tumor. The historical therapeutic strategy for advanced RCC relied on cytokines. Those drugs led to a response rate in the range of 10–15% and to a median overall survival (OS) of 10–12 months, while they were associated with substantial side effects [3]. The last decade witnessed important advances in the understanding of RCC molecular biology leading to a parallel development of several targeted agents and a remarkable improvement in treatment outcomes. Nowadays, half of the patients who are diagnosed with an advanced RCC are likely to survive more than two years.

Molecular biology

Clear cell renal cell carcinoma

Clear cell RCC (ccRCC) is more likely to occur sporadically than within a hereditary familial syndrome (95% and 5% of the cases, respectively) [4]. The Von Hippel-Lindau (VHL) syndrome is due to mutations occurring in the homonymous gene. This condition is associated with an increased risk of medical disorders like retinal angiomas, hemangioblastomas, and ccRCC (40–60% of the cases). Up to 90% of sporadic ccRCCs are related to an abnormal function of the *VHL* gene either through mutations or post transcriptional changes [5]. The understanding of this molecular pathway has provided the rationale for the further development of targeted therapies in ccRCC patients. The *VHL* gene encodes for a protein [pVHL] that regulates the level of expression of a transcription factor named hypoxia-inducible factor (HIF). HIF modulates the cellular response according to oxygen availability. In the situation of a normoxic environment, HIF interacts with pVHL and is therefore eliminated by ubiquitinization. Conversely, conditions of low oxygen or of deficiency in pVHL lead to an accumulation of HIF

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and transcription of genes related to the cellular adaptation to hypoxia. The transcription of those genes promote angiogenesis, cell growth and glycolysis through the activation of vascular endothelial growth factor (VEGF), transforming growth factor (TGF) alpha and beta and platelet derived growth factor (PDGF) [6]. Most of the innovative targeted therapies approved in advanced ccRCC target those proteins and their cognate receptors.

Analysis of more than 400 ccRCC samples by The Cancer Genome Atlas (TCGA) project showed data in the same direction. The most relevant genetic alterations in this tumor subtype were related to cellular oxygen sensing and include VHL and its related pathway members. Moreover a set of genes involved in chromatin modulation such as SETD2, KDM5C, PBRM1 and BAP1 appeared frequently mutated. Also, tumors more aggressive had an up-regulation of genes involved in fatty acid synthesis and glycolysis and down regulation of genes involved in Krebs cycle and almost a third of cases had mutations in the PI3K/AKT/mTOR signaling pathway. These results in combination with the data from gene expression will most likely serve as the basis for a future classification that will probably help in matching tumors and best treatment options [7,8].

Papillary tumours

A recent characterization of 161 primary papillary RCC (pRCC) in the TCGA project confirmed that type 1 and type 2 pRCC are not only clinically and pathologically diverse but also represent biologically different entities [9]. MET pathway alterations are more characteristic of type 1 pRCC. Conversely, activation of the NRF2–antioxidant response elements (ARE) pathway, CDKN2A silencing, SETD2 mutations and TFE3 fusions are characteristics of type 2 pRCC. A subgroup of these tumors with a particular poor prognosis and an association with fumarate hydratase (FH) mutations presented a CpG island methylator phenotype (CIMP). Based on these TCGA findings type 2 pRCC could be subdivided in at least three subtypes based on molecular and phenotypic features: IIa, IIb and CIMP profile.

Papillary type I renal cell carcinoma

The hereditary papillary RCC (HPRC) syndrome is an inherited condition that is associated with an increased risk of bilateral type I papillary RCC. The HPRC is due to an activating mutation occurring in the gene *MET* and located on the chromosome 7. As previously mentioned, recent characterization of the genomics of papillary RCC type I (pRCC) [9] has shown how even in the sporadic forms up to 81% of patients harbor alteration in *MET* either through mutation, splice variants, gene fusion or high copy number of chromosome 7. *MET* encodes for a transmembranal receptor of the hepatocyte growth factor (HGF). When binding to its receptor, HGF activates cellular pathways for proliferation through second messenger molecules like GRB2, GAB1 or PI3K. The activating mutation of *MET* leads to a permanent stimulation of its related receptor, independently of the binding of HGF. Yet, the development of papillary RCC tumors requires additional oncogenic events within the cell [10]. Here is the rationale for a therapeutic strategy targeting MET and its regulators in RCC, especially in papillary type I tumors [11].

Papillary type II renal cell carcinoma

The Hereditary Leiomyomatosis RCC (HLRCC) syndrome leads to the frequent development of papillary type II RCC. This familial syndrome is characterized by an aggressive type of kidney cancer, and by cutaneous and uterine leiomyomas [12]. The HLRCC condition is due to an inactivating mutation of the gene which encodes for the fumarate hydratase. This enzyme is part of the Krebs cycle and decreases the intracellular levels of fumarate. Conversely, when the fumarate hydratase is inactivated, the accumulation of fumarate prevents the degradation of HIF through hydroxylation. Moreover, the data obtained from the genomic analysis of sporadic forms of this tumor subtype trough the TCGA has shown its complexity. As commented above, type II pRCC could be divided in three subtypes with different genomics and clinical behavior known as: IIa, IIb and CIMP profile. These tumors are characterized by *CDKN2A* silencing, *SETD2* mutations, *TFE3* fusions, and increased expression of the NRF2–ARE. The CIMP tumors, that have a particularly poor prognosis and early onset, are characterized by genome-wide hypermethylation, *FH* mutations or low expression, and a shift to a Warburg-like metabolism.

Chromophobe renal cell carcinoma

The familial syndrome called Birt-Hogg-Dube (BHD) is due to an inherited and inactivating mutation of the homonymous gene, localized on the short arm of the chromosome 17. This condition is associated with an increased risk for different types of renal tumors, like hybrid oncocytic neoplasm (50%), chromophobe RCC [chRCC] (33%), ccRCC (10%) or oncocytoma (7%) [13]. Fibrofolliculomas are benign hair follicle tumors which are found in this syndrome in 85% of the cases. Pulmonary cysts are likely to be associated with spontaneous pneumothorax, and are diagnosed in more than 85% of the patients with BHD syndrome. The underlying germline mutation of the gene *BHD* occurs in around 90% of family members of a BHD patient [14].

The genomic analysis of sporadic chRCC cases published recently has revealed particular features for this subtype. chRCC typically presents with aneuploidy and massive elimination of chromosomal material. It harbors frequently TP53 mutations that are largely inactivating and appear combined with deletions on chromosome 17 (where BHD gene is located]. Also the loss of PTEN in association with deletions on chromosome 10 are common findings in this tumor type along with a high frequency of gene fusions involving the TERT promoter and an APOBEC-type mutational spectrum in a subset of tumours [15].

The gene *BHD* encodes for a protein named folliculin. This protein binds AMPH, and interacts with FNIP1 and FNIP2. This complex downregulates the activity of the mechanistic target of rapamycin (mTOR). The deficiency of folliculin increases the activity of mTOR pathway, leading to an upregulation of HIF [16]. Based on the previous data both mTOR and HIF pathways are seen as potential therapeutic targets.

Therapies in RCC

Approved drugs

Targeting VEGF/VEGFR

Angiogenesis is a key-target for the treatment of metastatic RCC (mRCC). Therapeutic strategies include the inhibition of the receptor of the vascular endothelial growth factor (VEGFR) by tyrosine kinase inhibitors and the blockade of the ligand itself (VEGF) by monoclonal antibodies (Fig. 1). Some anticancer drugs combining both effects have been developed recently.

Bevacizumab. Bevacizumab is an endovenous recombinant human monoclonal antibody that binds and neutralizes all the isoforms of VEGF which are biologically active [17]. Bevacizumab was the first antiangiogenic treatment to show clinical efficacy in advanced RCC. In a phase II trial, 116 patients with relapsing mRCC were randomized into three arms: placebo, low-dose (3 mg/kg), or high-dose of bevacizumab (10 mg/kg) every 2 weeks. The study findings