

An Update on Targeted Therapies in Renal Cell Carcinomas

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Abstract

The advancements in understanding of biological mechanisms in RCCs have led to the development and application of targeted therapies. The FDA approved targeted therapies are mainly directed against angiogenesis, mTOR pathways, and immune checkpoint inhibition. VEGF overexpression due to VHL gene mutation or alteration in majority of RCCs makes it one of the most suitable targets for development of therapy. Inhibitors and antibodies against VEGF or VEGFR have shown promising results in metastatic RCCs. mTOR pathway inhibition has also proven to be an efficacious strategy as well as antibodies targeting the immune checkpoints allowing T-Cells to attack tumour cells. However, there is need for improvement as certain proportion of patients may either not respond or develop resistance against targeted therapies.

Keywords: Angiogenesis inhibition; mTOR Pathway inhibition; Immune checkpoint inhibition; Mechanism of action; VEGF; VEGFR; mRCC

Introduction

Renal cell carcinomas (RCCs), arising from renal parenchyma, comprise 90% of the kidney cancers [1]. RCCs are chemotherapy and radiotherapy resistant. The mainstream treatment is surgery. Immunotherapy, including cytokines such as interferon- α (IFN- α) and interleukin 2 (IL-2), has shown some efficacy. However, the treatment has toxic side-effects [2]. In the recent years, the increased knowledge of underlying biological mechanisms in RCCs has led to the development and application of targeted therapies.

Targeted therapies approved by the US Food and Drug Administration (FDA) in the treatment of advanced RCC are listed in Table 1 [3]. These are directed against angiogenesis, mTOR pathways or immune checkpoints.

Angiogenesis inhibitors in RCCs

The mechanism of angiogenesis is a key target for the metastatic RCC (mRCC). More than 80% of sporadic RCC cases are caused by the disruption of the *VHL* gene [4]. pVHL deficiency results in hypoxia inducible factor (HIF) accumulation. Transcription of down-stream genes promotes angiogenesis, cell growth and glycolysis through the activation of vascular endothelial growth factor (VEGF), transforming growth factor (TGF) α and β , and platelet derived growth factor (PDGF). Most of the therapies approved in RCCs target these proteins and their corresponding receptors [5]. Therapeutic strategies in kidney cancer include the blockade of VEGF by monoclonal antibodies and the inhibition of VEGF receptor (VEGFR) by tyrosine kinase inhibitors. These antiangiogenic therapies may also be given in combination with conventional chemotherapy. Treatment options that target VEGF and VEGFR improve the progression free survival of patients with advanced RCC significantly to more than 26 months in recent randomized trials [6].

mTOR pathways inhibition in RCCs

The mammalian target of rapamycin (mTOR) is an intracellular signalling pathway in which mTOR is a protein kinase involved in the regulation of cellular functions such as proliferation, growth and survival. Rapamycin is an allosteric inhibitor of mTOR. Everolimus, a rapamycin analog (rapalog) has been approved by FDA for renal

cell carcinoma along with other specific cancers. Mostly, therapeutic effects lead to disease stabilization rather than tumor regression. Thus, combination treatments with chemotherapeutic or small molecule inhibitor agents are advised [7]. Temsirolimus is an anti-angiogenesis and mTOR inhibitor. By activation of mTOR, c-Myc, and HIF-1 α will be stimulated, which results in an increase in genes that promote VEGF-associated angiogenesis, proliferation (cyclin D1), and cell survival (survivin). The inhibition leads to decrease in concentration of down-stream targets [8].

Immune checkpoint inhibition antibodies in RCCs

Targeting inhibitory receptors on the surface of T-cells allows the immune system to attack tumour cells. Thus, antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell-death protein 1 (PD1), and PD-ligand 1 (PD-L1) have passed through clinical trials and succeeded to become one of the mainstream

Sr. No	Targeted therapy	Brand examples	Main mechanism of action
1	Axitinib	Inlyta [®]	Angiogenesis inhibition
2	Bevacizumab	Avastin [®] , Mvasi [™]	Angiogenesis inhibition
3	Cabozantinib	Cabometyx [™]	Angiogenesis inhibition
4	Everolimus	Afinitor [®]	m-TOR pathway inhibition
5	Lenvatinib mesylate	Lenvima [®]	Tyrosine kinase inhibitor
6	Nivolumab	Opdivo [®]	PD1-immune checkpoint inhibitor
7	Pazopanib	Votrient [®]	Angiogenesis inhibition
8	Sorafenib	Nexavar [®]	Angiogenesis inhibition
9	Sunitinib	Sutent [®]	Angiogenesis inhibition
10	Temsirolimus	Torisel [®]	m-TOR pathway inhibition

Table 1: FDA-approved targeted therapies in renal cell carcinomas.

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Received October 28, 2018; Accepted November 10, 2018; Published November 14, 2018

Citation: Ajaz S, Abid A (2018) An Update on Targeted Therapies in Renal Cell Carcinomas. J Mol Genet Med 12: 377 doi:10.4172/1747-0862.1000377

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therapies in cancers [9]. Nivolumab is a PD1 immune checkpoint inhibitor, which has been approved for mRCC [10].

Discussion and Conclusion

With the advent of these targeted agents, overall survival for RCC has improved. Patients are being treated continuously for increasingly long periods of time. However, these treatments rarely yield complete responses and are not curative. Therefore, search for suitable target(s) and development of specific therapies in RCCs must persist.

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