1 Introduction

Renal cell carcinoma (RCC) is the most frequent form of renal cancer and accounts for about 3% of adult cancers worldwide [1]. Generally, patients have a poor prognosis, and 12-25% of patients diagnosed with RCC bearing metastasis [2]. About 70% of patients diagnosed with localized advanced RCC. Unluckily, 20-40% of the patients will undergo recurrence and distant metastasis [3]. RCC affects mainly an elderly population with the peak incidence occurring between the ages of 60 and 70 [4]. Renal cancer cells are insensitive to chemotherapy and radiotherapy, with high likelihood of multidrug resistance [5].

Prior to 2005, the standard treatment for RCC was limited to cytokine therapy with IL-2 and/or IFN-α. These therapies are accompanied with limited efficacy and high toxicity [6]. Several newer targeted treatments are available for the treatment of patients with advanced conventional (clear cell) renal cell carcinoma (RCC), which received improved outcomes. These newer targeted treatments include the multi-targeted tyrosine kinase inhibitors (TKIs, sorafenib, sunitinib, pazopanib, and axitinib), the humanised antivascular endothelial growth factor (VEGF) monoclonal antibody [bevacizumab combined with interferon (IFN)-α], and mTOR (mammalian target of rapamycin) complex 1 kinase inhibitors (everolimus and temsirolimus). However, these targeted drugs are still associated with limited efficacy and high toxicity, so there is still a strong need for further discovery of new targeted drugs. In the present manuscript, we summarize newly-presented potential targeted drugs for RCC, classified by drug characteristic, small molecule, small molecule combination, monoclonal antibody, polysaccharides, organometals and peptides.

**Keywords:** renal cell cancer, targeted drug, small molecule drug, monoclonal antibody, drug combination
2 Small molecule drugs

2.1 (-)-antofine

(-)-antofine is a Met endosomal signaling inhibitor that inhibits nuclear translocation of STAT3. Song et al. [16] have reported that (-)-antofine has an effective function of inhibiting the proliferation of Met-mutated Caki-1 cells, which were resistant to currently known Met TKIs. (-)-Antofine disturbed Met endosomal signaling and as a result, inhibited the nuclear translocation of STAT3. Their findings revealed the potential role of Met endosomal signaling as a new target for Met T Ki-resistant renal cancers and (-)-antofine as a new lead compound with the inhibitory function on the Met endosomal signaling.

2.2 9-ING-41

9-ING-41 is a maleimide-based inhibitor of Glycogen synthase kinase-3 (GSK-3). GSK-3, a constitutively active serine/threonine kinase, is one of the key regulators of plentiful cellular processes ranging from cell-cycle regulation to glycogen metabolism. In accordance with its involvement in many pathways, it has been suggested in the pathogenesis of various human diseases, including, Alzheimer’s disease, bipolar disorder, inflammation, and cancer. Thus, it is recognized as a promising target for the development of novel targeted drugs. Pal et al. [17] have investigated the effect of 9-ING-41. They have shown that the anti-proliferative activity of 9-ING-41 is most likely caused by G(0)-G(1) and G(2)-M phase arrest as evident from cell-cycle analysis. They demonstrated the anti-tumor activity of 9-ING-41 in two different t RCC tumor models.

2.3 AZD2014

AZD2014 is a TORC1 and TORC2 inhibitor. Powles et al. [18] have conducted a randomised 49 patient phase II study of AZD2014 versus everolimus. The progression free survival (PFS) for AZD2014 and everolimus was 1.8 and 4.6 months, respectively (hazard ratio: 2.8 [95% confidence interval (CI), 1.2-6.5]; p = 0.01). Testing mTOR inhibitors with a broader spectrum of activity than everolimus in metastatic clear cell RCC is a strong rationale. In Powle’s study, they found that AZD2014 was inferior to everolimus, in despite of its toxicity advantages.

2.4 Chloroquine

Chloroquine is a 4-alkylamino substituted quinoline family member. It is an inhibitor of autophagy which can block the fusion of lysosomes and autophagosomes. Grimaldi et al. [19] have estimated the effects of everolimus in combination with chloroquine on RCC cell viability and revealed possible synergism. Their results suggest that RCC cells have different sensitivity to chloroquine and everolimus, and the pharmacological combination of chloroquine and everolimus had strong synergistic function on inducing the inhibition of cell viability.

2.5 Dovitinib

Dovitinib is an inhibitor of vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2). A phase Ib 18 patients study was conducted by Powles et al. [20]. They found that Everolimus (an mTOR inhibitor) and dovitinib present activity in metastatic clear cell RCC. Everolimus and dovitinib had moderate activity, but did not meet all of the planned efficacy end-points. The dose-limiting toxicity was fatigue in their study.

2.6 Ebselen

Ebselen is a synthetic organoselenium drug molecule with anti-inflammatory, anti-oxidant and cyto-protective activity. Quiescin sulphydryl oxidase 1 (QSOX1) is a highly conserved disulfide bond-generating enzyme which is overexpressed in multiple tumor types. QSOX1 promotes the growth and invasion of cancer cells and influences extracellular matrix composition. Hanavan et al. [21] had reported that, after mass spectrometric analysis of ebselen-treated QSOX1, they found that the C165 and C237 of QSOX1 covalently bound to ebselen. Their study depicts the anti-neoplastic properties of ebselen in renal cancer cell lines, providing a “proof-of-principle” that enzymatic inhibitory of QSOX1 may have clinical benefits.

2.7 Honokiol

Honokiol, which is isolated from Magnolia spp. bark, has been shown to possess anti-cancer effects in multiple cancer types. Li et al. [22] found that honokiol inhibited the metastasis of renal cancer cells via dual-perturbing epithelial-mesenchymal transition (EMT) and cancer stem cells (CSCs). Additionally, honokiol inhibited tumor cell proliferation.
in vivo. Honokiol could upregulate miR-141, which can target to ZEB2 and modulate ZEB2 expression. Honokiol reversed EMT and perturbed CSCs partly through the miR-141/ZEB2 axis. This study suggested that honokiol may be a promising therapeutic strategy for the treatment of RCC.

2.8 Metformin

Metformin (Met) is a hypoglycemic drug. It can inhibit the mitochondrial respiratory chain (complex I), activate AMP-activated protein kinase (AMPK), inhibit glucagon-induced promotion of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), and inhibit the activity of mitochondrial glycerophosphate dehydrogenase. Met (10 mM) treatment significantly increased the expression of Caspase-3 and Bax proteins in 786-O cells (human renal clear cell carcinoma cell line) [23]. Yang et al. also reported that metformin inhibits cell growth by up-regulating microRNA-26a in renal cancer cells [26]. Metformin may be a potential drug of choice in the treatment of metastatic RCC.

2.9 Nitidine chloride

Nitidine chloride (NC), a natural bioactive alkaloid derived from Zanthoxylum nitidum (Roxb) DC, has been shown to have inhibitory effects on various tumors. Fang et al. [25] demonstrated the proliferation-inhibitory and apoptosis-induced effects of NC on renal cancer cells both in vitro and in vivo. Using cell viability and flow cytometric apoptosis assays, Fang et al. found that NC can suppress the proliferation of 786-O and A498 cells in a time- and dose-dependent manner. Similarly, the xenograft model using nude mice exhibited disturbed tumor cell growth under NC treatment. NC significantly decreased phosphorylation of ERK and Akt, accompanied by up-regulation of P53, Bax, cleavage caspase-3 and cleavage PARP, downregulation of Bcl-2, caspase-3 and PARP. Their data imply that NC could be developed as a potential anticancer agent against renal cancer.

2.10 Rasfonin

Rasfonin is a fungal secondary metabolite with demonstrated antitumor effects. Lu, et al. reported that rasfonin enhanced autophagy. Akt up-regulated rasfonin-enhanced autophagy and caspase-dependent apoptosis dominantly through influencing the glycolytic pathway [26].

2.11 Ritonavir

Ritonavir is an inhibitor of human immunodeficiency virus protease and is also an inhibitor of CYP3A4. Sato et al. [27] have showed that ritonavir acted as a synergistic agent with panobinostat in enhancing histone acetylation and inhibiting renal cancer cell growth. Their study provides a basis for examining the combination of ritonavir and panobinostat for the treatment of advanced renal cancer.

2.12 S109

S109 is an inhibitor of chromosome region maintenance-1 (CRM1). Liu et al. found that S109 can inhibit the CRM1-mediated nuclear export of tumor suppressor protein RanBP1 and decreases the protein levels of CRM1, which indicates that CRM1 is a therapeutic target for the treatment of renal cancer and is a novel reversible CRM1 inhibitor. S109 could be a candidate for renal cancer therapy [28].

2.13 Saracatinib

Saracatinib is an inhibitor of tyrosine-protein kinase Src. Powles et al. [29] have conducted a randomized, double-blind phase II study evaluating cediranib versus a combination of cediranib and saracatinib in patients with relapsed metastatic clear-cell renal cancer. Saracatinib had no effect on increasing the efficacy of the VEGF-targeted therapy (cediranib therapy) in the study. There was no significant difference in progression free survival or overall survival between the patients who received cediranib and the combination of cediranib and saracatinib.

2.14 Simvastatin

Simvastatin is a cholesterol-lowering drug, inhibiting 3-hydroxy-3-methylglutaryl-coenzyme CoA (HMG-CoA) reductase. Woschek et al. [30] have reported the antiproliferative effects of simvastatin. The effect of simvastatin are not only mediated through cholesterol deprivation, but also through prenylation-associated mechanisms, therefore simvastatin, with its tumor-suppressive ability, could be a novel additive treatment option in the management of RCC.
2.15 Telmisartan

Telmisartan is a type of angiotensin receptor blocker (ARB). It is available to turnoff survival signaling through inhibiting anti-apoptotic molecules and suppressing caspase activity. De Araujo Junior et al. [31] reported that telmisartan induces apoptosis through decreased Bcl-2 and involved caspase-3 in human RCC.

2.16 Valproic acid (VPA)

Valproic acid (VPA) is a wide-spectrum inhibitor of class I and II histone deacetylases and presents great anti-cancer activity in multiple types of human cancer. Yang et al. [32] found that VPA obviously inhibited cell migration but not proliferation of human renal cancer ACHN cells. Mechanistically, they found that VPA can decrease the expression of HIF-1alpha. Knockout of HIF-1alpha inhibits cell migration, conversely, over-expression of HIF-1alpha markedly rescues the inhibitory effect of VPA. Further, they have found that the knockout of HDAC2 completely mimics the effects of VPA on HIF-1alpha and cell migration. Additionally, over-expression of HIF-1alpha could also rescue the effects of HDAC2 depletion on cell migration.

2.17 YM155

YM155 is a novel small molecule inhibitor of survivin. Koike et al. [33] have found that YM155 could abolish rapamycin resistance in a rapamycin-resistant RCC cells. Their results suggest that, in Caki-1-RapR cells (an induced rapamycin-resistant clear cell carcinoma cell line), YM155 significantly down-regulates survivin gene, protein expression and cell proliferation in a dose-dependent manner in vitro. The treatment with YM155 significantly abolished rapamycin resistance in the resistant cells. In tumor xenograft model using nude mouse, YM155 significantly inhibited the growth of Caki-1-RapR tumors. Additionally, YM155 significantly enhanced the antimetastatic effects of rapamycin in Caki-1-RapR tumors. Their results reveal that YM155 is a potentially novel strategy reverse the resistance in RCC.

2.18 Quercetin and hyperoside (QH)

Quercetin and hyperoside (QH) in combination (1:1 ratio) have previously been demonstrated to inhibit the proliferation of human leukemia cells. Li et al. [34] have examined the anti-cancer activity of the mixture in 786-O renal cancer cells. They found that QH mixture decreased the production of reactive oxygen species (ROS) and increased the antioxidant capacity in 786-O cells. QH mixture also induced caspase-3 cleavage and increased PARP cleavage. The treatment with QH mixture decreased the mRNA expression of Sp1, Sp3 and Sp4, which was accompanied by decreased protein levels. QH mixture can also down-regulate miR-27a and induce the zinc finger protein ZBTB10, which is an Sp-suppressor.

2.19 Bortezomib and belinostat

Belinostat is an inhibitor of histone deacetylase, and bortezomib is an inhibitor of proteasome. The accumulation of ubiquitinated protein and endoplasmic reticulum (ER) stress has recently been presented as a novel approach for the treatment of malignancies. Asano et al. [35] showed that belinostat increased the count of unfolded proteins through inhibiting heat-shock protein (HSP) 90, and that bortezomib inhibited their degradation via inhibiting the proteasome. As a result, bortezomib caused ubiquitinated protein accumulation and ER stress. Sato, A., et al. also reported that panobinostat synergizes with bortezomib [36]. They found that the mixture of panobinostat and bortezomib had a pro-apoptosis and growth inhibition function. It also suppressed colony formation. In a murine xenograft tumor model, 10-day treatment was well tolerated and suppressed tumor growth significantly. Increased acetylating of alpha-tubulin, a substrate of HDAC6, was consistent with the inhibition of HDAC6 by panobinostat, and the combination was presented to induce ER stress and ubiquitinated protein accumulation synchronously. Asano's and Sato's studies provides a basis for examining the combination of binostat and bortezomib in the treatment for advanced renal cancer.

3 Monoclonal antibody

3.1 Anti-S1P mAb

Zhang et al. [37] have demonstrated that a sphingosine-1-phosphate (S1P) antibody induced S1P inhibition may be a new therapeutic strategy in patients with RCC and also in the batching of resistance to TKI therapy.
3.2 Nivolumab

Immune-based therapies (e.g., IL-2, IFN) have been used for advanced clear cell RCC with overall moderate success. Recent studies have revealed that tumor cells escaped from immune-mediated destruction by inducing inhibitory signals, which result in effector T-cell exhaustion. Nivolumab, an anti-PD-1 antibody, blocks the interaction between the T-cell programmed death-1 (PD-1) receptor and its ligand, PD ligand-1. Michel Ortega et al [38] and Ozono [39] have reviewed the effect of the anti-PD-1 antibody, nivolumab, (ONO-4538/BMS-936558) on advanced renal cancer and have summarized the use of the new antibody drug in immunotherapy for renal cancer.

4 Polysaccharides, peptides, and organometals

4.1 BEP

BEP is a polysaccharide (Mw = 113,432 Da) purified from Boletus edulis, which has a backbone comprising of (1-->6)-linked-alpha-d-glucopyranosyl, (1-->2,6)-linked-alpha-d-galactopyranosyl, (1-->6)-linked-alpha-d-galactopyranosyl, and (1-->3)-linked-alpha-d-rhamnopyranosyl residues, which are branched at the O-2 position of the (1-->2,6)-linked-alpha-d-galactopyranosyl residue with a single terminal (1-->)-linked-alpha-l-arabinofuranosyl residue. Wang et al. [40] have showed BEP could significantly suppress the tumor mass of Renca transplanted in mice. Furthermore, BEP could significantly increase spleen and thymus indices, stimulate splenocyte proliferation, augment NK cell and CTL activity in spleen, and promote the secretion of the cytokines IL-2 and TNF-α in Renca tumor-bearing mice. Meanwhile oral administration of BEP (100 and 400 mg/kg) restored all altered hematological and biochemical parameters of tumor-bearing mice to normal levels. Thus, their data demonstrate that BEP possesses potential immunomodulatory activity and might serve as an effective therapeutic agent for the prevention of renal cancer.

4.2 Organometallic Titanocene-Gold Compounds

Organometallic Titanocene-Gold Compounds are early-late transition metal TiAu2 compounds [(eta-C5H5)2Ti(OC(O)CH2PPh2AuCl)(3) and [(eta-C5H5)2Ti(OC(O)-4-C6H4PPh2AuCl)(2)], (5). Fernandez-Gallardo et al. [41] evaluated the potential anticancer activity of the compounds. They found that the organometallic compounds were significantly more effective than monometallic titanocene dichloride and gold(I) [(HOC(O)RPPh2)AuCl] (R = -CH2- 6, -4-C6H4- 7) derivatives in renal cancer cell lines, suggesting a synergistic function of the resulting heterometallic species. The activity on renal cancer cell lines was considerably higher than that of cisplatin and highly activated titanocene Y. Further mechanistic studies in Caki-1 cells in vitro coupled with the studies of their inhibitory characters on a panel of 35 kinases of oncological interest suggest that these compounds inhibit protein kinase activities of the AKT and MAPK/APK families with a higher selectivity toward MAPKAPK3. Their studies suggest that these compounds (especially 5) are promising candidates for further development as potential renal cancer chemotherapeutics.

4.3 Acyldepsipeptide 1 (ADEP1)

Xu et al. [42] have found that ADEP1 induced renal cancer cell apoptosis through reducing the transcription of SHH and Gli-1, and decreasing Gli-1 and Bcl-2 protein expressions. ADEP1 could induce renal cancer cell apoptosis by the inhibition of SHH signaling pathway related proteins, suggesting a potential therapeutic strategy for RCC.

The targeted drugs that mentioned in this review are summarized in Table 1.

5 Discussion

Small molecule targeted drugs are still the main force in the treatment for RCC. In this review, we have summarized 17 small molecules, 2 small molecule combinations, 2 monoclonal antibodies, 1 polysaccharide, 1 organometal compound and 1 peptide for RCC. The emerging of biological drugs, such as peptides and antibodies, is expected. The drugs reviewed in this manuscript are mostly at an early stage of clinical application. Thus, this review can provide potential drugs for drug development and get insight into new therapeutic strategies for RCC.

Disclosure of conflict of interest: Authors declare nothing to disclose.
Table 1. The targeted drugs that mentioned in this review.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Drug Characteristic</th>
<th>Target</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-antofine</td>
<td>small molecule</td>
<td>Met endosomal signaling/nuclear translocation of STAT3</td>
<td>RCC resistant to well-known Met TKIs</td>
</tr>
<tr>
<td>9-ING-41</td>
<td>small molecule</td>
<td>Inhibition of GSK-3</td>
<td>RCC</td>
</tr>
<tr>
<td>AZD2014</td>
<td>small molecule</td>
<td>TORC1 and TORC2</td>
<td>VEGF-refractory mRCC</td>
</tr>
<tr>
<td>chloroquine</td>
<td>small molecule</td>
<td>blocks the fusion of autophagosomes and lysosomes</td>
<td>RCC</td>
</tr>
<tr>
<td>dovitinib</td>
<td>small molecule</td>
<td>Inhibition of VEGF and FGF-2</td>
<td>VEGF-refractory clear cell RCC</td>
</tr>
<tr>
<td>Ebselen</td>
<td>small molecule</td>
<td>Quinescin sulfhydryl oxidase 1 (QSOX1)</td>
<td>pancreatic cancer and RCC</td>
</tr>
<tr>
<td>Honokiol</td>
<td>small molecule</td>
<td>Through mIR-141/ZEB2 axis</td>
<td>RCC</td>
</tr>
<tr>
<td>metformin</td>
<td>small molecule</td>
<td>Inhibition of the mitochondrial respiratory chain (complex I)</td>
<td>mRCC</td>
</tr>
<tr>
<td>Nitidine chloride</td>
<td>small molecule</td>
<td>Suppressing ERK signaling pathway</td>
<td>RCC</td>
</tr>
<tr>
<td>Rasfonin</td>
<td>small molecule</td>
<td>Inhibits human immunodeficiency virus protease and CYP3A4</td>
<td>advanced renal cancer</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>small molecule</td>
<td>Reduces Chromosome region maintenance-1 (CRM1)</td>
<td>NR</td>
</tr>
<tr>
<td>Saracatinib</td>
<td>small molecule</td>
<td>Inhibitor of Src kinase</td>
<td>RCC</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>small molecule</td>
<td>3-hydroxy-3-methylglutaryl-coenzyme CoA (HMG-CoA reductase</td>
<td>RCC</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>small molecule</td>
<td>Inhibition of angiotensin receptor</td>
<td>RCC</td>
</tr>
<tr>
<td>Valproic acid (VPA)</td>
<td>small molecule</td>
<td>Inhibits histone deacetylases</td>
<td>RCC</td>
</tr>
<tr>
<td>YM155</td>
<td>small molecule</td>
<td>Inhibition of survivin</td>
<td>Rapamycin-resistant RCC</td>
</tr>
<tr>
<td>quercetin and hyperoside</td>
<td>small molecule combination</td>
<td>Inhibition of oncogenic microRNA-27a</td>
<td>RCC</td>
</tr>
<tr>
<td>Bortezomib/ belinostat</td>
<td>small molecule combination</td>
<td>Inhibition of proteasome/histone deacetylase</td>
<td>advanced renal cancer</td>
</tr>
<tr>
<td>anti-S1P mAb</td>
<td>monoclonal antibody</td>
<td>Sphingosine-1-phosphate (S1P)</td>
<td>Naive and VEGF-refractory RCC</td>
</tr>
<tr>
<td>nivolumab</td>
<td>monoclonal antibody</td>
<td>Anti-PD-1 antibody</td>
<td>Advanced renal cancer</td>
</tr>
<tr>
<td>BEP</td>
<td>polysaccharide</td>
<td>Inhibition of AKT and MAPKAPK families</td>
<td>RCC</td>
</tr>
<tr>
<td>Titanocene-Gold</td>
<td>organometal</td>
<td>Inhibition of AKT and MAPKAPK families</td>
<td>RCC</td>
</tr>
<tr>
<td>Acyldepsipeptide 1 peptide</td>
<td></td>
<td>reducing the transcription of SHH and Gli-1</td>
<td>RCC</td>
</tr>
</tbody>
</table>

References


NEWLY PRESENTED POTENTIAL TARGETED DRUGS IN THE TREATMENT OF RENAL CELL CANCER

129


