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REVIEW ARTICLE

New therapeutic approaches in the management of metastatic renal cell carcinoma

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Summary

Renal cell carcinoma (RCC) accounts for approximately 2% of all cancers worldwide. For several decades cytokine therapy using either interleukin-2 (IL-2) or interferon -alpha (IFN-α) was the only effective treatment available for patients with metastatic RCC. Metastatic RCC represents a chemotherapy- and radiotherapy-resistant tumor with poor prognosis and 5-year survival rate <10%. Over the past few years considerable advances in the understanding of biology and underlying molecular pathways in RCC have resulted in the development of targeted therapies for this disease.

Key words: immunotherapy, metastatic, renal cell carcinoma, targeted therapy

Introduction

RCC is the most common cancer of the kidney accounting for approximately 2-3% of all malignant diseases and ranking 10th as leading cause of cancer-related deaths in humans. In Europe, approximately 40,000 patients are diagnosed with RCC each year, leading to an estimated 20,000 deaths [1,2]. In 85% of them the tumor originates from cells of the proximal tubules and is known as Grawitz tumor, hypernephroma or renal cell carcinoma.

At the time of diagnosis about 25% of the patients have disseminated disease and another 20% will have locally advanced disease [3]. RCC is a tumor with high metastatic potential. 5-year survival of patients with advanced disease is <10%. So far nephrectomy represents the first-line treatment for resectable RCC, or even for metastatic RCC (cytoreductive nephrectomy). Until recently the aim of treatment of advanced or metastatic RCC was palliation with nephrectomy, chemoembolization or radiation. Since RCC is highly resistant to chemotherapy, IL-2 or IFN-α are widely used as first-line treatment of metastatic disease. Clinical response rates to these cytokines are low (5-20%) and median survival is approximately 9-15 months, while the rate of adverse events is high. IFN-α has shown a modest but statistically significant benefit in terms of overall survival and high-dose bolus IL-2 is associated with durable complete remissions in about 7% of the patients [4,5]. A major spin off from the randomized trials in the cytokine era has been the recognition of prognostic factors. At present, the most frequently used model is the one developed by Motzer et al. (Memorial Sloan-Kettering Cancer Center/MSKCC) criteria [6]. Three patient groups were discerned on the basis of 5 factors (Karnofsky performance status <80, lactate dehydrogenase >1.5 the upper limit of normal, haemoglobin level below the lower limit of normal, corrected serum calcium >10 mg/dl and absence of nephrectomy). This scoring system has since been widely used in clinical studies to group patients in good, intermediate and poor risk categories with significantly different survival times.

Recently, advances in the understanding of molecular biology have allowed the identification of various pathways that, when targeted, can impede the growth of RCC. A key target in RCC is the pathway mediated by the vascular endothelial growth factor (VEGF), which triggers angiogenesis. Several agents that target this pathway, including sorafenib, sunitinib, bevacizunab, temsirolimus and others have recently demonstrated efficacy in RCC.

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Molecular biology of RCC, Von Hippel-Lindau syndrome and VEGF

Distinct subtypes of RCC are defined on the basis of specific oncogenes or genetic abnormalities. Clear cell carcinoma is the most common form of RCC and its commonest molecular lesion is the inactivation of the Von Hippel-Lindau (VHL) tumor suppressor gene.

This gene is inactivated in up to 80% of clear cell carcinomas, either by deletion, mutation or methylation. Von Hippel-Lindau syndrome is characterized by a germline mutation of chromosome 3p and a predisposition to subsequent development of RCC [7,8]. Non-inherited clear cell RCC characterized by VHL gene inactivation results in the constitutive expression of the oxygen-regulated transcription factor hypoxia inducible factor-α (HIF-α), the induction of hypoxia-inducible genes, including VEGF, platelet derived growth factor (PDGF) and subsequent promotion of tumor angiogenesis [9].

Under hypoxic conditions or when the VHL protein is mutated, HIF-α is not degraded. Constitutively expressed HIF-α upregulates about 200 genes including VEGF and PDGF, promoting angiogenesis and allowing cancer growth (Figure 1).

The concept of VEGF inhibition in RCC was brought to the oncology community by Yang et al. in a report that demonstrated clinical benefit with the use of anti-VEGF monoclonal antibody bevacizunab in the treatment of RCC [10]. Shortly, the small molecule tyrosine kinase inhibitors sunitinib and sorafenib were also shown to be active in RCC. Clear cell RCC is clinically recognized as a highly vascularised tumor. VEGF messenger RNA expression correlates with this vascularisation, and VEGF is overexpressed in the vast majority of patients with RCC of the clear-cell subtype [11,12]. The VEGF pathway consists of a transmembrane receptor with an extracellular portion that binds the VEGF protein. The VEGF receptor (VEGFR) family has at least 4 members, but the key mediator of angiogenesis is VEGFR-2. Once VEGFR-2 has bound the VEGF ligand, a conformational change takes place that allows autophosphorylation of the receptor. This initiates a cascade of phosphorylation events that promote gene upregulation and leads to angiogenesis [13,14].

Tyrosine kinase inhibitors

Tyrosine kinases are enzymes that provide a central switch mechanism in cellular signal transduction pathways. As such they are involved in many cellular processes such as cell proliferation, metabolism, survival and apoptosis. Several tyrosine kinases are known to be activated in cancer cells and to drive tumor growth and progression. Blocking tyrosine kinases' activity therefore represents a rational approach to cancer therapy. Therapeutic strategies include blocking ki-

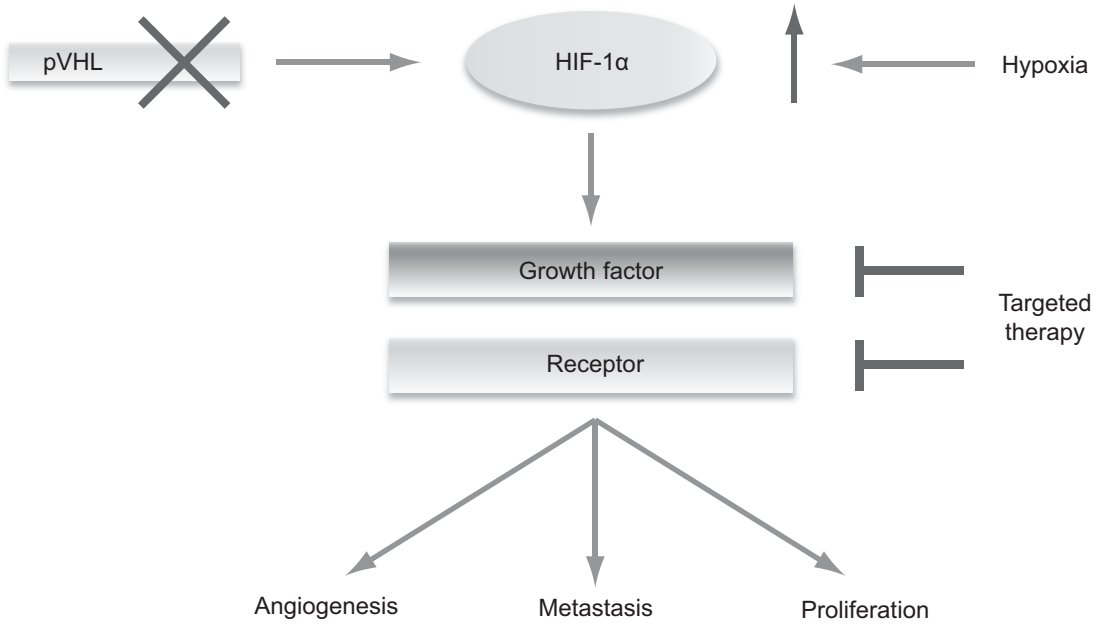

Figure 1. Schematic illustration of the activation of the transcription factor hypoxia-inducible factor-1α (HIF-1α) in clear cell renal carcinoma due to loss of von Hippel-Lindau protein (pVHL) function and hypoxia. As a result, increased expression of growth factors and activation of their receptors lead to increased cell survival, stimulates proliferation and angiogenesis and promotes metastasis (Modified from Storkel et al. [7]).

nase-substrate interaction, inhibiting the enzymes' adenosine triphosphate (ATP) binding site and blocking extracellular tyrosine kinases' receptors in tumor cells. Several tyrosine kinase inhibitors (TKIs) have already been approved as anticancer agents.

Sunitinib

Sunitinib is an oral multitargeted receptor TKI of vascular endothelial growth factor receptor (VEGFR1-2-3), platelet-derived growth factor receptor (PDGFR α and β), c-Kit protein and FLT3 receptors [15,16]. All these tyrosine kinase receptors play key roles in the pathogenesis of clear cell carcinoma, which is the predominant type of RCC. Sunitinib was approved for the treatment of advanced RCC in January 2006. Presumably, sunitinib inhibits tumor growth by inhibiting VEGF and PDGF signaling pathways as well as other signaling pathways [17].

Motzer and colleagues reported an objective response rate of 42% in a pooled analysis of 2 phase II trials of sunitinib that far exceeded previously reported response rates for cytokines when used as first-line therapy [16,18]. Recently, sunitinib has been compared to IFN-α in the treatment of metastatic RCC in patients who had not received any prior systemic therapy [19]. Patients in the study had measurable disease, ECOG (Eastern Cooperative Oncology Group) performance status of 0 and 1 and adequate haematologic, coagulation, hepatic, renal and cardiac function. Both sunitinib and IFN-α were given at standard doses. Sunitinib was given orally once daily at a dose of 50 mg for 4 weeks followed by 2 weeks without treatment. IFN-α was injected subcutaneously 3 times a week on nonconsecutive days at 3 MU per dose during week 1, 6 MU per dose during week 2 and 9 MU per dose thereafter. Treatment was continued until disease progression or unacceptable toxicity. The median progression-free survival (PFS) was 11 months for sunitinib and 5 months for IFN-α. This corresponded to a hazard ratio of 0.42 in favor of sunitinib and was statistically highly significant (p=0.001). In the sunitinib group, 13% of patients died vs. 17% in the IFN-α group (p=0.02). The median PFS with sunitinib was longer in intermediate and poor risk patients as assessed by the Motzer et al. criteria. Adverse events were mild (grade 1 or 2) and included fatigue, nausea, diarrhea, hypertension, anaemia, and hand-foot syndrome [19].

Sorafenib

Sorafenib was identified because of its inhibitory effect on Raf-1, a serine-threonine kinase, VEGFR2, PDGFR, FMS-like tyrosine kinase3 (FLT-3) and c-kit. Sorafenib has demonstrated broad spectrum antitumor activity in a number of tumor xenograft models, including renal cell adenocarcinoma [20].

The FDA approved sorafenib for treatment of advanced RCC in December 2005, based on the results of 2 phase II trials. In the first study Ratain and colleagues performed a phase II randomized discontinuation trial. In this study all patients initially received oral sorafenib 400 mg twice daily, then those with stable disease at 12 weeks were randomly assigned to sorafenib or placebo. It was observed that most patients who responded to sorafenib had clear cell RCC [21]. At 24 weeks 50% of the sorafenib-treated patients had stable disease compared with only 18% of the placebo-treated patients (p=0.0007). Sorafenib also extended median PFS compared with placebo. Similarly, the TARGET study (Treatment Approaches in Renal Cancer Global Evaluation Trial) from Escudier et al. was designed to clarify the impact of sorafenib on PFS and overall survival in patients with clear cell RCC, who had been previously treated with cytokine therapy [22]. All patients had clear cell RCC and unresectable or metastatic disease. Patients were randomized to receive sorafenib or placebo as second-line therapy. The stable disease rate in this study was 78% for the sorafenib group vs. 55% in the placebo group (p <0.001; Table 1). In addition, PFS was 5.5 months in the sorafenib-treated patients vs. 2.8 months in the placebo group (p <0.01), so PFS was approximately doubled with sorafenib. The most common side effects (grade 1or 2) in both studies were skin rash, nausea, hand-foot syndrome, fatigue, hypertension and diarrhea.

Bevacizumab

Bevacizumab was the first antiangiogenic agent to be approved for the treatment of a human cancer (colorectal). This humanized recombinant anti-VEGF monoclonal antibody was created by transferring the VEGF-binding regions of a murine antibody to a humanized IgG1 framework, resulting in a 93% human

Table 1. TARGET study [22]

Response	*Sorafenib (n=335) n (%)*	*Placebo (n=337) n (%)*
Partial response	7 (2)	0 (0)
Stable disease	261 (78)	186 (55)
Progressive disease	29 (9)	102 (30)
Missing	38 (11)	49 (15)

and 7% murine molecule. Bevacizumab has a linear pharmacokinetic profile with a half-life of 21 days and the dose of 10 mg/kg is considered safe and well tolerated [23]. The first study with bevacizumab that showed a significant clinical benefit was a randomized phase II, placebo-controlled, blind study in patients with metastatic RCC [10]. In this study evaluated were 116 patients who were randomly assigned to one of 3 groups: placebo (n=40), or bevacizumab 3 mg/kg (n=37) or 10 mg/kg (n=39) every 2 weeks. The median time to progression was 2.2, 3.0 and 4.8 months respectively ($p < 0.001$ for the 10 mg/kg dose vs. placebo). Four (10%) patients in the 10 mg/kg group had a partial response. Overall survival was not statistically different, although there did appear to be a trend towards improved survival in bevacizumab-treated patients. Bevacizumab 10 mg/kg every 2 weeks is currently evaluated in 2 large double blind phase III studies with IFN-α 9MIU, 3 times weekly as the comparator. The AVOREN study in Europe is closed and data will become available soon [24]. An early press release of this study indicated a positive result regarding PFS. The addition of bevacizumab to IFN-α2α significantly increased PFS (10.2 vs. 5.4 months), and objective tumor response rates (30.6 vs. 12.4%) with a trend toward improved overall survival (p=0.067). CALGB-90206 is an ongoing phase III trial in the USA that will recruit 700 patients with advanced RCC. Patients receive either INF-α2β or IFN-α2β plus bevacizumab 10 mg/kg on days 1 and 15 of a 4-week cycle. The primary endpoint is survival. The trial is expected to last 3 years [25].

Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR), which had shown antitumor activity in preclinical studies. In a phase II study of 111 patients with advanced refractory RCC, an objective response was observed in 7% and minor responses in 26% [26].

The essential difference from the angiogenesis inhibitors is that mTOR inhibitors have a direct effect on the tumor cell.

Based on a series of phase I and II studies, a randomized phase III study in poor risk patients has been completed, which compared single-agent IFN-α, single-agent temsirolimus (25 mg), or both agents combined [27,28]. Patients treated with temsirolimus monotherapy experienced a median survival of 10.9 months vs. 7.3 for IFN-α (p=0.007) and 8.4 for the combination. Median PFS was 3.7 vs. 1.9 and 3.7 months, respectively. More than 70% of patients had poor-risk features according to the MSKCC risk score. An analysis of the influence of tumor histology on treatment outcome suggested that although the benefit of temsirolimus was seen both in patients with clear cell and non-clear cell histology, the benefit of temsirolimus was most pronounced in those with non-clear cell RCC [29]. The most prominent adverse events attributable to temsirolimus were stomatitis, peripheral oedema, nausea and rash. All these side effects were manageable and reversible [29].

Second-line therapy of metastatic RCC

Axitinib

Axitinib is an imidazole derivative that inhibits the tyrosine kinase portion of all VEGFRs and PDGFR-β at low concentrations [30]. In a recent phase II study [31] of axitinib (5 mg twice daily) in patients with sorafenib-refractory metastatic RCC, partial response was observed in 6 of the 42 evaluable patients (14%) and stable disease in 15 (36%). Disease progression occurred in 12 patients (29%) and 9 patients (21%) were withdrawn from the study due to adverse events. The most common adverse effects in trials with axitinib as a single-agent have included fatigue, proteinuria, stomatitis/mucositis, raised blood pressure and diarrhea.

Everolimus

Everolimus (RAD001) is an oral mTOR inhibitor which has shown activity in a phase II trial of patients with RCC [32]. In this trial patients with no more than 1 prior therapy (n=41) received everolimus 10 mg/day in a 28-day cycle. Twelve (23%) patients exhibited a partial response and 19 (46%) stable disease for more than 3 months. Everolimus is also under investigation in a randomized phase III trial [33] in patients with mRCC who progressed during treatment with sunitinib and/or sorafenib. Common adverse events in the study included mouth ulcers, high blood lipids, high blood sugar, skin rash, anemia, low phosphate levels, and inflammation of the lungs.

Lapatinib

The efficacy of lapatinib**,** a dual inhibitor of EGFR (ErbB-1 and ErbB-2 type I receptor tyrosine kinase [RTKs]), has been compared with hormone treatment (tamoxifen and megestrol acetate) in a phase III study in patients with advanced RCC after failure of first-line cytokine therapy [34]. Overall median time to progres-

sion and median overall survival did not differ significantly between the two treatment groups. However, patients with high EGFR expression showed improved median time to progression in the lapatinib group and median overall survival was significantly longer in these patients (46 weeks) than in similar patients receiving hormone treatment (37.9 weeks, p=0.02). This study shows that patient selection may be important to optimize lapatinib treatment. The most common side effects of lapatinib have included fatigue, indigestion, skin rach, vomiting and diarrhea.

Conclusion

Due to recent advances in the understanding of molecular biology, RCC has become one of the most exciting areas of cancer research. Several novel agents that target signaling pathways are in development and have recently been approved for the treatment of RCC. Results with several of these targeted agents confirm that inhibiting multiple tumor targets is an effective approach to treatment, offering improved results for the future management of RCC. The latest studies focus on combining these agents with other novel therapies or more conventional treatments, such as cytokines, to evaluate their use in the adjuvant and front-line metastatic settings. In addition, other targeted agents such as mTOR and angiopoietin-2 (Ang-2) are also under investigation. These novel agents are likely to become the cornerstone of therapy as we enter a new treatment era for metastatic RCC.

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