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Molecular Pathways in Metastatic Renal Cell Carcinoma: The Evolving Role of Mammalian Target of Rapamycin Inhibitors

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Abstract

Context: Metastatic renal cell carcinoma (mRCC) is particularly resistant to conventional treatments. Improved understanding of the molecular pathways involved in mRCC has led to the development of novel targeted therapies for this disease.

Objective: This review describes key molecular pathways that have emerged as therapeutic targets for mRCC. Particular emphasis is placed on the mammalian target of rapamycin (mTOR) pathway and the newer class of targeted agents (ie, mTOR inhibitors).

Evidence acquisition: Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.

Evidence synthesis: The von Hippel-Lindau (VHL) tumour suppressor gene was discovered in 1993 and has a vital role in renal cell carcinoma (RCC) pathogenesis. *VHL* mutations lead to accumulation of hypoxia-inducible factors (HIFs) that stimulate overexpression of the proangiogenic vascular endothelial growth factor (VEGF). The mTOR pathway was subsequently identified, which regulates cell growth, proliferation, and angiogenesis, and also has a pivotal role in RCC. An increase in HIF expression is a product of the mTOR pathway. Therefore, agents that suppress the mTOR pathway have become the focus of much research. Such mTOR inhibitors as everolimus and temsirolimus have shown robust clinical efficacy in treating mRCC. For example, everolimus has proved effective in patients whose disease has progressed after treatment with VEGF-targeted therapy.

Conclusions: Targeted agents against components of the mTOR pathway are in clinical use and have improved outcomes for patients with advanced disease and poor prognosis or with advanced disease that has become refractory to sunitinib or sorafenib.

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1. Introduction

Metastatic renal cell carcinoma (mRCC) is one of the most treatment-resistant malignancies, characterised by diverse clinical manifestations and associated with extremely poor clinical outcomes [1]. Surgery and chemotherapy have limited or no effect once the disease has progressed to the advanced stage. In addition, poor outcomes with cytokine-based therapies leave these patients with an unmet clinical need for alternative therapeutic options. In the past decade, elucidation of the genetic and molecular bases of mRCC has been accompanied by the development of a number of novel targeted therapies that are now approved for the treatment of this disease. Many other agents are in preclinical development or in ongoing clinical trials, offering hope of further improvements in treatment outcomes and prognoses for patients with mRCC.

In this review, we describe the major molecular pathways that have emerged as relevant therapeutic targets for mRCC, with a focus on the role of one of the newer classes of targeted agents, namely the mammalian target of rapamycin (mTOR) inhibitors.

2. Evidence acquisition

Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.

3. Evidence synthesis

3.1. Von Hippel-Lindau gene mutations

The von Hippel-Lindau (VHL) tumour suppressor gene has a pivotal role in the pathogenesis of renal cell carcinoma (RCC) [2,3]. Mutations in this gene are responsible for VHL syndrome, a hereditary condition characterised by an increased risk of developing bilateral clear cell RCC. A breakthrough in understanding the molecular basis of RCC was the discovery that in the majority of nonhereditary (sporadic) clear cell RCCs, the tumour suppressor protein encoded by *VHL* is functionally inactive, primarily as a result of genetic mutation or DNA hypermethylation [4,5]. Mutations of *VHL* result in the accumulation of hypoxia-inducible factor (HIF), which, in turn, stimulates angiogenesis through overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [6,7].

3.2. Targeting the von Hippel-Lindau/hypoxia-inducible factor pathway

The discovery of the association between *VHL* inactivation, upregulation of proangiogenic genes, and the subsequent progression of RCC provided relevant therapeutic targets for the development of novel treatments [8]. The first to be approved in this indication was the tyrosine kinase inhibitor (TKI) sorafenib, which inhibits VEGF receptor (VEGFR), PDGF receptor (PDGFR), and Raf kinase, a component of the mitogen-activated protein kinase/extracellular-signal-regulated kinase pathway, which is crucial in maintaining control of cell proliferation [9]. The approval of sorafenib was soon followed by approval of another antiangiogenic TKI, sunitinib, a small-molecule inhibitor that targets both VEGFR and PDGFR. The efficacy observed in phase 3 clinical trials [10–13] led to these therapies becoming standards of care and being incorporated into national and international clinical practice guidelines [14,15]. These agents are now being investigated in combination regimens [16,17] and in the adjuvant setting [18,19] in an effort to further define their place in the treatment algorithm for mRCC.

Bevacizumab, a humanized recombinant monoclonal antibody that binds to VEGF and blocks its interaction with VEGFR, has been shown to provide a modest level of partial responses when used as a monotherapy in mRCC [20]. Although bevacizumab monotherapy appeared to have less efficacy than multitargeted TKIs, impressive response rates have been observed when bevacizumab was used in combination with interferon [21,22] or sorafenib [23]. Its combination with other therapies, such as sunitinib, may be precluded because of an increased level of toxicity above that expected with the use of each agent alone [24].

3.3. Role of the mammalian target of rapamycin pathway in renal cell carcinoma

Another major pathway involved in the pathogenesis of RCC is the mTOR pathway (Fig. 1). This pathway regulates cellular proliferation and metabolism in response to environmental factors, linking cell growth factor receptor signalling via phosphoinositide-3 kinase (PI3K) to cell growth, proliferation, and angiogenesis [25]. A strong association between the PI3K pathway and the oncogene phosphatase and tensin homologue (*PTEN*) has also been established. Loss of *PTEN* function through mutation, although rare in RCC, or epigenetic silencing results in increased activation of the protein kinase Akt and mTOR. This, in turn, results in enhanced activity of eukaryotic translation initiation factor 4E binding protein and p70 ribosomal protein S6 kinase, the net effect of which is to stimulate cellular protein synthesis and entry of cells into the G1 phase of the cell cycle. Another product of the mTOR pathway, and of particular relevance to RCC, is an increase in HIF-1α and HIF-2α expression, both of which regulate angiogenesis [26]. It is postulated, therefore, that suppression of mTOR may be a means of reducing angiogenesis, and several agents targeting the mTOR pathway have entered clinical development. Unlike sorafenib and sunitinib, which inhibit the HIF pathway distally by blocking HIF effectors such as VEGF and PDGF, mTOR inhibitors such as everolimus and temsirolimus act proximally by inhibiting mTOR kinase activity and decreasing levels of HIF. Furthermore, because the mechanism of action of mTOR inhibitors in mRCC is distinct from other targeted agents, a rationale exists for investigating these drugs in patients whose disease has progressed after treatment with a VEGF-targeted therapy.

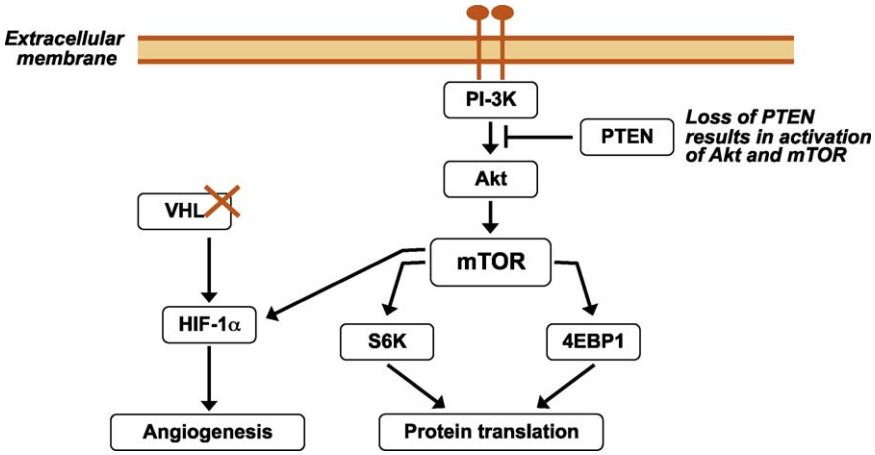

Fig. 1 – The mammalian target of rapamycin (mTOR) signalling pathway and its interaction with the von Hippel–Lindau (VHL)/hypoxia-inducible factor-1α (HIF-1α) pathway.
4EBP1 = 4E-binding protein-1; PI-3K = phosphoinositide-3 kinase; PTEN = phosphatase and tensin homologue; S6K = S6 kinase.

3.4. *Targeting the mammalian target of rapamycin pathway*

Temsirolimus (CCI-779) is an intravenously administered mTOR inhibitor. Phase 2 trials have shown survival benefit in cytokine-refractory patients after treatment with temsirolimus [27]. Temsirolimus became the third drug in <2 yr to be approved by the European Medicines Agency for the treatment of advanced RCC. Approval was largely based on the results of a multicentre phase 3 trial comparing the efficacy of temsirolimus alone and in combination with interferon (IFN)-α in poor-prognosis patients with advanced RCC [28]. In this study, a total of 626 patients with previously untreated, poor-prognosis mRCC were randomised to receive temsirolimus alone (25 mg weekly), temsirolimus (15 mg weekly) plus IFN-α (6 million U three times weekly), or IFN-α alone (3 million U [with an increase to 18 million U] subcutaneously three times weekly). Poor prognosis was defined using a modification of the Memorial Sloan-Kettering Cancer Centre model, with patients required to have three or more of the following predictors of short survival: a serum lactate dehydrogenase level >1.5 times the upper limit of normal range, a haemoglobin level below the lower limit of normal range, a corrected serum calcium level >10 mg/dl, a time from initial diagnosis to randomisation of <1 yr, a Karnofsky performance score of 60 or 70, and metastases in multiple organs. Temsirolimus alone provided the greatest benefits in terms of improved overall survival (OS; 10.9 mo vs 7.3 mo; $p = 0.008$) and progression-free survival (PFS; 3.8 mo vs 1.9 mo; $p < 0.001$), compared with IFN-α alone (Fig. 2). Median OS in the group receiving both temsirolimus and IFN-α did not differ significantly from that in the IFN-α alone group (8.4 mo vs 7.3 mo; $p = 0.70$). The objective response rate was also greater in the temsirolimus group (8.6%) than in the IFN-α group (4.8%) and combination group (8.1%), although none of these differences were significant.

Temsirolimus showed a generally favourable safety profile. The most frequently occurring adverse events at any grade in patients receiving this treatment alone were asthaenia (51%; grade ≥3, 11%), rash (47%; grade ≥3, 4%), anaemia (45%; grade ≥3, 20%), and nausea (37%; grade ≥3, 2%). Thrombocytopaenia (14% vs 8%), stomatitis (20% vs 4%), peripheral oedema (27% vs 8%), and infection (27% vs 14%) at any grade occurred more frequently in the temsirolimus group than in the IFN-α group. In addition, hyperglycaemia (26% vs 11%), hyperlipidaemia (27% vs 14%), and hypercholesterolaemia (24% vs 4%) at any grade were also more frequently reported in the temsirolimus group than the IFN-α group, possibly owing to an inhibitory effect of temsirolimus on mTOR regulation of glucose and lipid metabolism. Grade 3 or 4 adverse events occurred in 67% of patients in the temsirolimus group, compared with 78% of patients in the IFN-α group ($p = 0.02$) and 87% of patients in the combination-therapy group ($p = 0.02$). Fewer serious adverse events were reported in the temsirolimus group than in the IFN-α group ($p = 0.02$). Pneumonitis, an adverse event associated with mTOR inhibitors, was not reported in this trial, although grade ≥3 dyspnoea was reported in 9% of the temsirolimus group and in 6% of the IFN-α group.

Temsirolimus was the first, and to date the only, targeted agent to demonstrate a significant improvement in the primary end point of OS in poor-prognosis patients and has since been recommended instead of sunitinib as a first-line therapy for poor-prognosis patients.

The orally administered mTOR inhibitor everolimus has shown promising antitumour activity in vivo and antiproliferative activity against tumour cells in vitro [29]. Furthermore, the effect of mTOR inhibition by everolimus on tumour vascular biology was similar to, but distinct from, VEGF pathway inhibition, demonstrating their differing mechanisms and the potential use of mTOR inhibitors as second-line treatments [29]. Everolimus has been evaluated in multiple tumour types, including mRCC. A phase 2 trial with everolimus demonstrated promising antitumour activity in patients with mRCC, including those pretreated with cytokines [30,31]. Furthermore, everolimus demonstrated antitumour activity in patients with mRCC

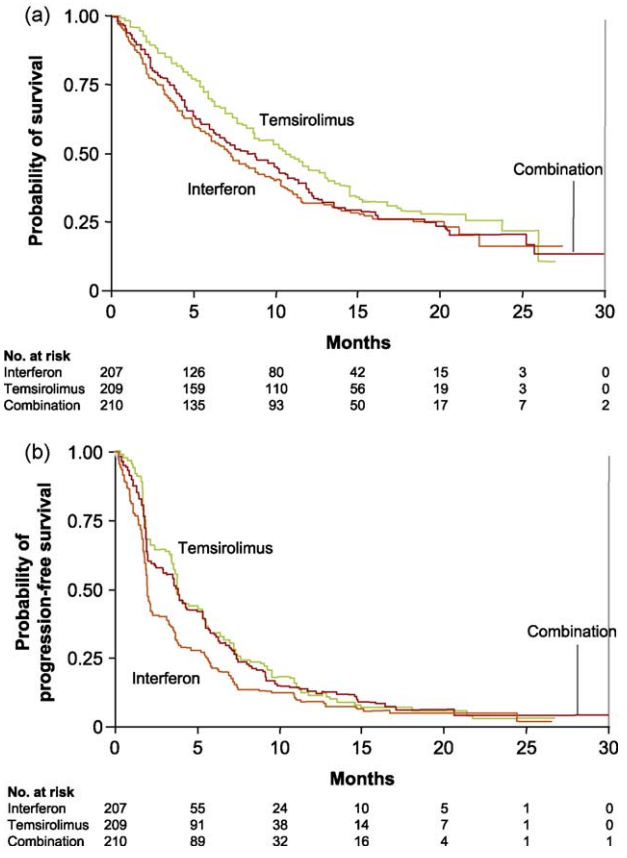

Fig. 2 – Kaplan–Meier estimates of (a) overall survival and (b) progression-free survival of patients with metastatic renal cell carcinoma treated with temsirolimus, interferon-α, or both. Reproduced with permission from the Massachusetts Medical Society [28].

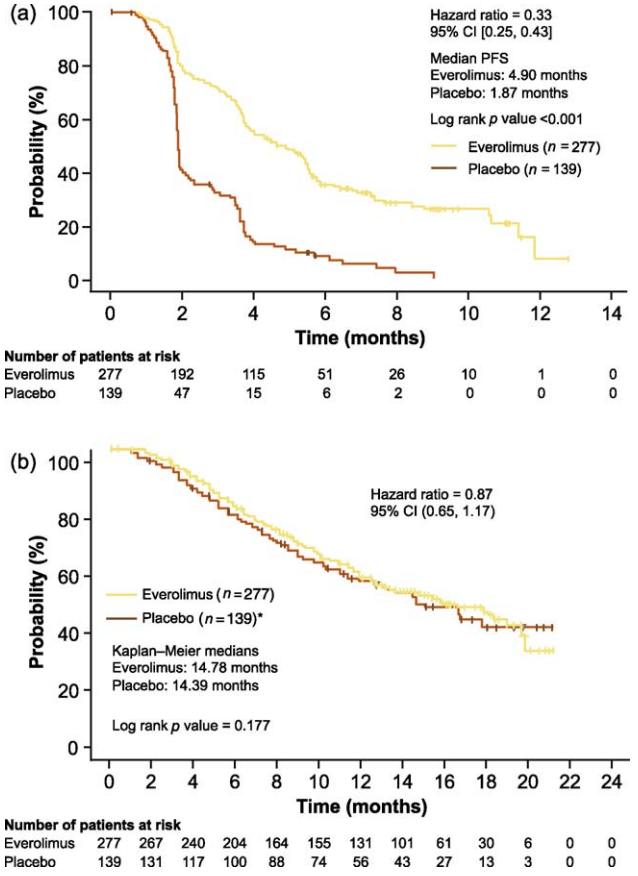

Fig. 3 – Kaplan–Meier estimates of (a) progression-free survival (PFS) and (b) overall survival of patients with metastatic renal cell carcinoma treated with everolimus or placebo. Note: *112 of 139 patients randomised to placebo were treated with open-label everolimus. Reproduced with permission from the American Society of Clinical Oncology [35].
CI = confidence interval.

previously treated with sorafenib or sunitinib [32]. The potential of everolimus as a treatment option for patients refractory to a VEGF-targeted therapy has been investigated in the Renal Cell Cancer Treatment with Oral RAD001 Given Daily (RECORD-1) trial, the largest phase 3 trial to be conducted in this subgroup of patients for whom subsequent therapeutic options are limited. RECORD-1 was a randomised, phase 3, double-blind, placebo-controlled, multicentre trial in patients with mRCC who had failed prior treatment with a VEGF-targeted therapy [33]. Patients who progressed on placebo as determined by investigator assessment were allowed to cross over to receive open-label everolimus. Significantly favourable median PFS was observed in patients receiving everolimus compared with placebo (second interim analysis [$n = 410$]: 4.0 mo vs 1.9 mo, $p < 0.0001$ [33]; end of double-blind analysis [$n = 416$]: 4.90 mo vs 1.87 mo, $p < 0.001$ [34]; Fig. 3a). At the time of the second interim analysis, median OS for everolimus-treated patients had not yet been reached, but the median survival for placebo recipients was 8.8 mo [33]. At the end of double-blind analysis, median OS was 14.78 mo in the everolimus group and 14.39 mo in the placebo group [35] (Fig. 3b). No significant difference between the groups in terms of OS (hazard ratio, 0.87; $p = 0.177$ [35]) was observed, although this was probably because of confounding of the end point by crossover: 81% of placebo recipients who progressed as determined by investigator assessment crossed over to open-label everolimus; 76% of the patients who crossed over had progressed within 8 wk of enrolment [33]. The median time to decline of Karnofsky performance status and Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms risk score was prolonged with everolimus compared with placebo (5.78 mo vs 3.84 mo, $p = 0.004$, and 4.76 mo vs 3.84 mo, $p = 0.053$, respectively) [35].

In addition, everolimus showed a relatively favourable safety profile. At the end of double-blind analysis, the most frequently occurring adverse events, mostly grade 1 or 2 in severity, were stomatitis (40% of patients receiving everolimus vs 8% of patients receiving placebo), rash (25% vs 4%), fatigue (20% vs 16%) or asthaenia (18% vs 8%), and diarrhoea (17% vs 3%) [33]. Other treatment-related adverse events included infections (10% vs 2%) and noninfectious pneumonitis (8% vs 0%). Laboratory abnormalities included hypercholesterolaemia (76% vs 32%), hyperglyceridaemia (71% vs 30%), and hyperglycaemia (50% vs 23%).

Everolimus is the first and only agent to demonstrate significant clinical benefit in patients with mRCC after failure of a VEGF-targeted therapy. Recent approval by the US Food and Drug Administration (FDA; March 2009) was granted for use in patients with advanced RCC after treatment failure with sunitinib or sorafenib. European Union approval for use of everolimus in patients with advanced RCC whose disease progressed on or after treatment with VEGF-targeted therapy was granted in August 2009.

Inhibiting a single tumourigenic signalling pathway with one therapy may be less effective than using a combination of agents to target multiple molecular pathways. Using this approach, mTOR inhibitors could potentially overcome resistance to VEGF-targeted therapies. Combining mTOR inhibitors with other targeted therapies may also overcome potential resistance to mTOR inhibition [36]. Resistance may potentially arise from positive feedback signalling through mTOR complex 2 leading to Akt activation. This could limit the therapeutic effects of mTOR inhibitors, which selectively inhibit only mTOR complex 1 (TORC1). Furthermore, loss of feedback inhibition of PI3K signalling resulting from TORC1 inhibition could also potentially limit the antitumour activity of mTOR inhibitors. In addition, an mTOR-independent mechanism downstream of PI3K signalling may compensate for mTOR inhibition.

The relatively favourable safety profile of everolimus facilitates its combination with other targeted agents, and a number of studies have been conducted or are currently under way. PTK787/ZK222584 (vatalanib), a multitargeted kinase inhibitor against VEGFR and PDGFR, was well tolerated in combination with everolimus and demonstrated clinical activity in patients with RCC despite previous exposure to VEGF inhibition [37]. More recently, results from a phase 1 study of everolimus in combination with sorafenib have also shown promising antitumour activity and tolerability [38]. In addition, a phase 2 study of the combination of everolimus and bevacizumab has shown that full doses of both agents could be given and that the combination was generally well tolerated with promising efficacy results [39]. Further studies using this combination are planned. Other potential combination and sequential treatment approaches are discussed elsewhere in this supplement [40].

4. Conclusions

The last decade witnessed remarkable improvements in our understanding of the genetic and molecular bases of RCC. Important therapeutic targets were identified, and novel agents were developed that rapidly underwent clinical testing. The HIF/VEGF pathway and the mTOR signal transduction pathway have emerged as relevant therapeutic targets and have been the focus of much research. Drugs targeting components of these pathways are now in clinical use, some as standards of care. Furthermore, data emerging from clinical trials in patients with advanced disease suggest that targeted therapy is likely to continue improving treatment options and outcomes, thereby helping to reduce the unmet medical needs of these patients.

The addition of mTOR inhibitors to the treatment options available for mRCC is an exciting new development and represents a significant advance in the treatment of this challenging disease. Recently approved in the United States by the FDA (with Europe expected to follow), it is anticipated that the oral mTOR inhibitor everolimus will become an important agent, not only in patients who have progressed on VEGF-targeted therapy but also as an efficacious component of combined therapeutic approaches.

Conflicts of interest

Dr. Ravaud is a member of the Global, European, and/or French board for Bayer, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth for urologic tumours. Institutional funding support for research was obtained from Novartis, Roche, and GlaxoSmithKline. Dr. Wallerand has no conflicts of interest. The authors did not receive an honorarium or consultancy fee for writing this paper.

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