Review

Tyrosine Kinase and Mammalian Target of Rapamycin Inhibitors in the Treatment of Advanced Renal Cell Carcinoma: Practical Clinical Implications of Pharmacologic Features

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Abstract

The development of multiple vascular endothelial growth factor- and mammalian target of rapamycin-targeted therapies in advanced renal cell carcinoma has resulted in significant clinical benefit. However, the availability of multiple treatment options has led to a more complicated clinical decision-making process. Prognostic factors have been incorporated into the inclusion criteria for pivotal clinical trials and have thus provided some guidance regarding the selection and sequencing of therapy. Even within a given patient risk group and particular line of therapy, questions remain regarding the optimal choice of a targeted agent. The present review provides a practical, clinician-oriented assessment of pharmacologic factors that should be considered when a receptor tyrosine kinase or mammalian target of rapamycin kinase inhibitor is used to treat patients with advanced or metastatic renal cell carcinoma. Although these 2 classes of agents have different mechanisms of action, they are metabolized by similar pathways, resulting in broadly similar pharmacokinetic and drug–drug interaction profiles. To further individualize therapy and optimize clinical benefit, an enhanced understanding of the key pharmacologic features that differentiate these agents is important.

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Introduction

According to the most recent estimates, approximately 338,000 patients are newly diagnosed with kidney cancer worldwide annually and > 143,000 patients die of this disease.[1] In the United States, it was predicted that 61,560 new cases of kidney cancer, of which renal cell carcinoma (RCC) is the most common type, would be diagnosed in 2015, with 14,080 deaths.[2] In addition, RCC has been ranked as the 7th and 10th most common malignancy in US men and women, respectively.[2] Up to 30% of patients with newly diagnosed RCC will present with metastatic disease at diagnosis.[3,4] Moreover, ≤ 40% of patients initially treated for localized disease will eventually develop systemic metastatic disease.[3,5]

In 1992, the US Food and Drug Administration (FDA) approved the cytokine interleukin-2 (IL-2) for the treatment of advanced RCC, based on durable complete responses seen in approximately 5% of patients.[6,7] Until only recently, high-dose IL-2 and interferon (IFN) were widely used as first-line treatment of metastatic RCC. However, both of these treatments have been associated with significant toxicity, and the clinical efficacy has been relatively modest, with low response rates (5%-20%) and a median overall survival (OS) lasting approximately 12 months.[6-10] The era of targeted therapy began with the US FDA approval of the receptor tyrosine kinase inhibitors (TKIs) sorafenib (Nexavar; Bayer Healthcare Pharmaceuticals, Wayne, NJ; Onyx Pharmaceuticals, San Francisco, CA) and sunitinib (Sutent; Pfizer Inc, New York, NY) in 2005 and 2006, respectively. Since 2006, 4 additional targeted agents, as outlined in Table 1, have been approved for advanced or metastatic RCC, and these agents include temsirolimus (Torisel; Pfizer Inc, New York, NY), everolimus (Afinitor; Novartis Pharmaceuticals Corp, East Hanover, NJ), pazopanib (Votrient; GlaxoSmithKline,

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Table 1 Dosage, Administration, and Pharmacologic Targets of TKIs and mTOR Inhibitors Used for Treatment of Metastatic and/or Advanced RCC

Agent (Trade Name)	Administration	Recommended Dose and Schedule	Dosage Forms and Strengths	Targets (IC_{50})
TKIs				
Sorafenib[11,12] (Nexavar)	Oral	400 mg b.i.d. without food	200-mg tablets	Raf-1 (0.006 μM), WT B-raf (0.022 μM), mutant B-raf (0.038 μM), c-KIT (0.068 μM), FLT-3 (0.058 μM), RET (0.047 μM), VEGFR-1, -2, and -3 (0.026, 0.090, and 0.020 μM, respectively), and PDGFR-β (0.057 μM)
Sunitinib[13-15] (Sutent)	Oral	50 mg/day on schedule 4/2 with or without food	12.5-, 25-, and 50-mg capsules	c-KIT (~0.001-0.01 μM), FLT-3 (~0.25 μM), RET (0.05 μM), VEGFR-1, -2, and -3 (0.015, 0.038, and 0.030 μM, respectively), PDGFR-α and -β (0.069 and 0.055 μM, respectively), and CSF-1R (0.05-0.1 μM)
Pazopanib[16,17] (Votrient)	Oral	800 mg/day without food	200-mg tablets	VEGFR-1, -2, and -3 (0.010, 0.030, and 0.047 μM, respectively), PDGFR-α and -β (0.071 and 0.084 μM, respectively), c-KIT (0.074 μM), FGFR-1, -3, and -4 (0.14, 0.13, and 0.8 μM, respectively), and c-Fms (0.146 μM)
Axitinib[18,19] (Inlyta)	Oral	5 mg b.i.d., ~12 h apart with or without food	1- and 5-mg tablets	VEGFR-1, -2, and -3 (0.001, 0.002, and 0.001-0.003 μM, respectively)
mTOR inhibitors				
Temsirolimus[20,21] (Torisel)	IV	25 mg infused over a 30-60-min period once a week	25 mg/mL supplied with diluent	mTOR (1.76 μM)
Everolimus[22,23] (Afinitor)	Oral	10 mg daily consistently with or without food	2.5-, 5-, 7.5-, and 10-mg tablets	mTOR (FKBP12; 0.0016-0.0024 μM)

Abbreviations: c-Fms = transmembrane glycoprotein receptor tyrosine kinase; c-KIT = stem cell factor receptor; CSF-1R = colony stimulating factor receptor type 1; FGFR = fibroblast growth factor receptor; FLT-3 = fms-related tyrosine kinase 3 receptor; IC_{50} = half maximal inhibitory concentration; IV = intravenous; mTOR = mammalian target of rapamycin; PDGFR-β = platelet-derived growth factor receptor-β; RET = glial cell-line derived neurotrophic factor receptor rearranged during transfection; RTK = receptor tyrosine kinase; schedule 4/2, 4 weeks of treatment followed by 2 weeks without treatment; VEGFR = vascular endothelial growth factor receptor; WT = wild-type.

Research Triangle Park, NC), and axitinib (Inlyta; Pfizer Inc). The biologic rationale for each of these agents for RCC is well-established, providing support for their clinical development and subsequent use in everyday clinical practice. In addition to the small-molecule TKIs and inhibitors of mammalian target of rapamycin (mTOR) kinase discussed in the present review, bevacizumab (Avastin; Genentech, South San Francisco, CA), a neutralizing monoclonal antibody against vascular endothelial growth factor (VEGF), was approved in combination with IFN for advanced RCC in July 2009.[24,25] Cabozantinib, an inhibitor of MET, VEGF receptor (VEGFR), and other tyrosine kinases, demonstrated improved progression-free survival (PFS) versus everolimus in patients with advanced RCC with progression after previous VEGF-targeted therapy.[26]

Immune checkpoint inhibitors, such as the anti-programmed death-1 monoclonal antibody nivolumab, are also being evaluated in clinical trials for advanced RCC and have shown promising clinical activity. For example, an open-label phase III study of nivolumab in patients with previously treated metastatic RCC (CheckMate 025; n = 821) was recently stopped early because the data and safety monitoring committee concluded that the study had met its primary endpoint, demonstrating superior OS with nivolumab over everolimus (hazard ratio [HR], 0.73; 98.5% confidence interval [CI], 0.57-0.93; $P = .002$), with a median OS of 25.0 and 19.6 months, respectively.[11] In November 2015, nivolumab was approved by the US FDA for patients with advanced RCC who have received previous anti-angiogenic therapy.[13]

The main histologic RCC subtype is clear cell, which is characterized by deletions and inactivating mutations in the von Hippel-Lindau (*VHL*) gene. These mutational events result in loss of VHL protein function, elevated hypoxia inducible factor (HIF)-1α and HIF-2α levels, and subsequent overexpression of several key growth factors that promote tumor angiogenesis, including VEGF and platelet-derived growth factor (PDGF).[27] Sorafenib, sunitinib, pazopanib, and axitinib are all multitargeted inhibitors with varying potency and selectivity against VEGFR, PDGFR, and other receptor tyrosine kinases. Temsirolimus and everolimus are small-molecule mTOR kinase inhibitors[28] (Table 1). Abnormal mTOR signaling is thought to contribute to increased HIF expression and abnormal angiogenesis, and evidence for mTOR activation has been observed in up to two thirds of patients with metastatic clear cell RCC.[29]

The rapid development and availability of multiple targeted therapies has led to greater challenges for the practicing oncologist with regard to clinical decision-making. Within a given risk group and specific line of therapy, questions remain as to which small molecule should be selected.[20,22,30] The objective of the present review was to provide a practical, physician-oriented assessment of the key pharmacologic factors that should be considered when a TKI or an mTOR inhibitor is used to treat patients with advanced RCC.

Sorafenib

Key Clinical Data

Sorafenib was approved by the US FDA in December 2005 for advanced RCC based on the results of the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), a randomized phase III study (and a previous phase II randomized discontinuation trial that included patients with metastatic RCC).[12,14,16,18]