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Metastatic clear cell renal cell carcinoma: A review of current therapies and novel immunotherapies

Jacob S. Thomas, Fairooz Kabbinavar*

University of California, Los Angeles, 924 Westwood Blvd. Suite 1050, Los Angeles, CA 90023-7207, USA

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ABSTRACT

Treatment of metastatic renal cell carcinoma (mRCC) has changed dramatically in the past 10 years, largely due to advances in understanding of tumor biology. A number of targeted therapies have been shown to improve progression free survival and overall survival as compared to nonspecific immunotherapy. Despite the success of targeted therapies, they have not produced durable responses that have been seen historically with immunotherapy such as IL-2 (interleukin 2) and IFN-α (interferon). The promise of durable responses has caused some to shift research focus from targeted therapies to novel immunotherapies. This article reviews the literature behind the current targeted therapies and describes several novel approaches to immunotherapy that are in various phases of development.

1. Introduction

In the past ten years metastatic renal cell carcinoma (mRCC) has changed from a fatal disease with few therapeutic options to a chronic progressive disease with several tiers of therapeutic options. The American Cancer Society estimates that in 2014 there will be 63,920 new diagnoses of kidney cancer and 13,860 deaths, comprising from 3 to 5% of all adult malignancies in the United States (Siegel et al., 2014). The incidence of renal cell carcinoma has been rising, which includes both early stage and late stage disease (King et al., 2014). Approximately 85% of all RCC are clear cell tumors (Karumanchi et al., 2002). The remaining subtypes of RCC include papillary, chromophobe, and oncocytoma, as well as other

* Corresponding author at: University of California, Los Angeles, 924 Westwood Blvd. Suite 1050, Los Angeles, CA 90023-7207. Fax: +1 310 794 3512.
E-mail address: fkabbina@mednet.ucla.edu (F. Kabbinavar).

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minor subtypes. About 20–30% of patients have metastatic disease at the time of diagnosis, and about 20% will develop metastatic disease after being diagnosed with early stage disease (Ljungberg et al., 2011). mRCC was historically known to have low response rates to cytotoxic chemotherapy, which prompted research for novel treatments (Yagoda et al., 1993; Amato, 2000).

Spontaneous tumor regressions in mRCC have been reported, which suggests that RCC is an immunogenic tumor (Lokich, 1997). It has also been observed that immune cells often infiltrate RCC tissue, which suggests a role of the adaptive immune system (Attig et al., 2009; Schendel et al., 1993). These findings led to non-specific immunotherapy trials with Interleukin-2 (IL-2) and interferon (IFN-α). These treatments had response rates up to 30% with durable response rates up to 7%, however due to the toxicity of treatment this has been used in only select patients (Rosenberg et al., 1994; Fisher et al., 2000; Fosså, 2000). For many years immunotherapy remained the only effective treatment option for mRCC. Recent efforts have been made to identify predictive pathologic features to improve response rates. Unfortunately, no marker has yet been identified that predicts response rates (McDermott et al., 2014).

As with other tumor types, advances in therapy of mRCC have resulted from increased understanding of tumor biology and genetics. The majority of research has been focused on clear cell RCC (ccRCC). A strong basic science foundation regarding RCC led to development of targeted therapies that have altered the natural course of the disease. However, despite the success of the targeted therapies median overall survival for mRCC remains between roughly 11–26 months (Escudier et al., 2007a,b; Motzer et al., 2006, 2010; Sternberg et al., 2010). Thus, novel treatment strategies are needed to further improve outcomes for these patients.

Because immunotherapy with IL-2 and IFN-α remain the only therapies with consistent, although rare, durable response, there has been recent increased interest in the development of novel immunotherapeutic strategies.

This review will cover clinically relevant advances in the molecular biology of ccRCC, focusing on current and potential future targets for therapy. Data regarding current standard first and second line therapies will be discussed. Finally, novel immunotherapies currently in development will be discussed. Treatment issues for non-clear cell renal cell carcinoma are beyond the scope of this review.

2. Molecular biology behind targeted therapy of RCC

Early understanding of RCC genetics began with the identification of the familial form of RCC associated with the Von Hippel–Lindau (VHL) disease. VHL disease is an autosomal dominant neoplastic disorder with variable penetrance (Maher et al., 2011). The VHL gene was identified in 1993 and found to be a tumor suppressor gene, which is also present in sporadic forms of RCC (Latif et al., 1993; Leung and Ohh, 2002). Patients with VHL disease are born with a germ-line mutation in one allele and develop tumors as a result of acquiring a mutation in the second allele in the affected tissue, in accordance to Knudson's two-hit theory. The product of the VHL gene, pVHL, was found to be involved in targeting the α subunit of hypoxia-inducible factor (HIF1α) for ubiquitin-mediated proteasomal degradation. HIF1α is a transcription factor that regulates oxygen-dependent gene expression (Leung and Ohh, 2002). Under hypoxic conditions HIF1α binds with HIF1β to form the HIF complex that activates expression of several genes including vascular endothelial growth factor (VEGF), erythropoietin (EPO), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and carbonic anhydrase IX (CAIX). (Harris, 2002) Inactivation of pVHL through mutation leads to constitutive activation of the HIF complex and upregulation of these and other genes that are oncogenic and allow for cell proliferation. This understanding led to interest in antiangiogenesis therapies targeting VEGF that have led to much of the success in mRCC treatment over the past decade.

As this VEGF pathway became better understood and was targeted, attention then turned to other pathways that could yield potential targets for mRCC therapy. One of the most important targets found upstream of the VEGF pathway is the mammalian target of rapamycin (mTOR). mTOR is a kinase that is involved in regulating cell energy and nutrition levels, cell-cycle progression, as well as response to hypoxic stress through the HIF1α pathway (Bjornsti et al., 2004). Because mTOR was also involved in angiogenesis through the HIF1α/VEGF pathway it was a natural target for mRCC therapy.

3. current standard targeted therapies

Over the past ten years, five agents have been approved for first-line therapy in mRCC, and two more have been approved as second-line agents. Most of the first-line agents have similar efficacies, therefore selection is based on side effect profiles as well as practitioner reference. The following is a chronological discussion by when each agent was approved for use and does not reflect an order of preference.

3.1. Sorafenib

The first VEGF-specific therapy to be approved for mRCC was sorafenib. Sorafenib is a tyrosine kinase inhibitor (TKI) that targets the VEGF receptors (VEGFR) 1–3, the PDGF receptor β (PDGFRβ), the c-Kit protein (c-Kit), FMS-like tyrosine kinase 3 (Flt-3), and the RET proto-oncogene. In a 2007 phase 3, double blind, randomized controlled trial (RCT) Sorafenib was shown to have statistically significant improved median progression free survival (PFS) compared to placebo. The study included 903 patients with mRCC that progressed despite standard therapy, which at that time was non-specific immunotherapy. PFS was 5.5 months in the sorafenib arm and 2.8 months in the placebo arm. There was a trend towards improved overall survival (OS) at 19.3 months; however, this was not statistically significant, thought to be due to crossover effect as patients in the placebo arm were eventually offered sorafenib. Common adverse events (AE) included hypertension, hand–foot syndrome, diarrhea, nausea, rash, and alopecia (Escudier et al., 2007a). Sorafenib was later studied as a first line agent in 2009. In a phase 2, open-label, randomized trial sorafenib was compared to IFN-α in previously untreated patients. Sorafenib and IFN-α had similar PFS (5.7 months vs. 5.6 months, respectively), but sorafenib-treated patients had greater rates of tumor size reduction, better quality of life, and improved tolerability (Escudier et al., 2009).

3.2. Sunitinib

Shortly after sorafenib was approved sunitinib was also approved. Sunitinib is a TKI with targets similar to sorafenib. In 2007 a phase 3 RCT compared sunitinib to IFN-α in patients diagnosed with mRCC and no prior treatment with systemic therapy. Sunitinib showed superior PFS compared to IFN-α (11 months vs. 5 months). There was a 31% objective response rate and 48% of patients with stable disease. Patients also reported better quality of life with sunitinib compared to IFN-α. Common AEs with sunitinib included diarrhea, vomiting, hand–foot syndrome, hypertension, and cytopenias. The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the IFN-α group (Motzer et al., 2007). Long term follow up of this trial showed