

Recent advances in management of renal cancer

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Abstract

Therapeutic options for patients with metastatic renal cell carcinoma have significantly improved over the past few years, resulting in prolonged progression-free and overall survival.

Introduction and context

Renal cell carcinoma (RCC) is the sixth leading cause of cancer deaths in developed nations [1]. Until recently, immunotherapy with interferon-alpha (IFN- α) and interleukin-2 were the only therapies available for patients with advanced disease, with major response rates typically seen in 10-15% of patients. Most patients died of their disease within 1 to 2 years of developing metastases. Identification of the VHL (Von Hippel-Lindau) tumor-suppressor gene and the discovery that its inactivation in clear cell RCCs leads to increased expression of hypoxia-inducible factor-alpha (HIF- α) and angiogenesis related proteins, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) B chain, led to the development of new therapies that specifically target VEGF signaling pathways. Multiple effective agents are now available that prolong progression-free survival (PFS) and/or overall survival in phase III randomized studies. These agents have become the standard care for most patients.

Recent advances

Bevacizumab, a humanized VEGF-neutralizing antibody, was the first VEGF-targeted therapy to show activity in metastatic RCC [2]. Two multicentered phase III studies compared bevacizumab plus IFN- α to IFN- α alone as first-line treatment in patients with metastatic RCC [3,4]. Both studies demonstrated a significant improvement in PFS in patients receiving bevacizumab (10.2 versus 5.4 months and 8.5 versus 5.6 months) as well as an increase in the objective tumor response rate (30.6% versus 12.4% and 25.5% versus 13.1%). Based on these

trials, bevacizumab plus IFN- α has recently been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic RCC.

Sunitinib is an oral tyrosine kinase-inhibitor that targets VEGF receptors, PDGF receptors, the Fms-like tyrosine kinase (FLT)3 and the c-KIT receptor tyrosine kinase. Sunitinib first demonstrated antitumor activity in cytokine refractory patients with a median time-to-progression of 8.7 months [5]. A randomized phase III trial compared sunitinib with IFN- α in patients with previously untreated metastatic clear-cell RCC [6]. In this trial, patients treated with sunitinib demonstrated a 31% objective response rate and a median PFS and overall survival of 11 and 26.4 months, respectively, while patients treated with interferon experienced a 6% objective response rate, a 5-month median PFS, and a 21.8-month median overall survival [7].

Sorafenib is another multikinase inhibitor designed as a c-Raf and b-Raf kinase inhibitor, but it also inhibits VEGF receptors, PDGF receptors, FLT3 and KIT. A phase III randomized study of sorafenib compared with placebo for second-line therapy in cytokine-refractory RCC patients showed that patients receiving sorafenib had a significantly prolonged median PFS compared with placebo (24 versus 12 weeks) [8].

A randomized phase II trial of first-line treatment with sorafenib (400 mg twice daily) compared with IFN- α for previously untreated patients with clear-cell RCC demonstrated no significant difference in PFS

(5.7 months versus 5.6 months) [9]. Despite the perception that older patients are at higher risk for toxicity effects and may obtain less clinical benefit from cancer treatment, sorafenib treatment demonstrated similar PFS and overall efficacy for both older and younger patients with advanced RCC. In addition, the frequency, severity, and quality of life of sorafenib-related toxicities were similar between the two age groups [10].

Clinical studies have also successfully targeted rapamycin, a protein kinase responsible for protein translation, cell growth, and apoptosis. The mammalian target of rapamycin (mTOR) protein is frequently activated in RCC, which can result in increased production of HIF-1 α . Two current ester analogues of rapamycin, temsirolimus and everolimus, in addition to rapamycin itself, have shown antitumor activity. A recent phase III trial evaluating the PFS of orally administered everolimus versus placebo in patients who progressed on at least one VEGF-targeted therapy demonstrated a median PFS of 4 months versus 1.9 months in the placebo patient group [11].

This study was the first phase III randomized trial to demonstrate efficacy of second-line therapy for patients who progress on a VEGF inhibitor. Temsirolimus, which is administered intravenously weekly, was previously FDA-approved based on the results of a randomized trial of temsirolimus and IFN- α in patients with poor risk RCC, with a median overall survival of 10.9 months in patients receiving the mTOR inhibitor compared with 7.3 months for patients receiving IFN- α alone [12].

Implications for clinical practice

The therapeutic options for patients with metastatic RCC have greatly increased with the development of drugs targeting the VEGF and mTOR pathways. Variability in trial design and eligibility criteria for the multiple studies can make it difficult to compare results and to determine if one agent is superior as first- or second-line therapy. Furthermore, differences in the clinical effects and toxicities of these agents as well as characteristics of individual patients may affect a physician's choice of therapy. There are currently potentially many different treatment approaches for each patient with metastatic RCC with the universal goal of prolonging survival [13,14]. Several clinical trials designed to determine if a specific combination or sequence of agents is superior have recently been opened. These include the BeST trial (ECOG E2804), which is a randomized phase II study of various combinations of bevacizumab, sorafenib and temsirolimus in patients with advanced RCC. In addition, the ASSURE trial (Adjuvant Sorafenib or Sunitinib

for Unfavorable Renal Carcinoma) is designed to determine if adjuvant therapy has a role in patients who have undergone nephrectomy. Unfortunately, the results of these studies are unlikely to be available for a number of years.

Abbreviations

ASSURE, Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; FDA, US Food and Drug Administration; FLT3, Fms-like tyrosine kinase 3; HIF, hypoxia-inducible factor; IFN- α , interferon alpha; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor receptor; PFS, progression free survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; VHL, Von Hippel-Lindau.

Competing interests

The authors declare that they have no competing interests.

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