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Seminar article

Systemic adjuvant therapy for renal cell carcinoma: Any hope for future clinical trials?

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Abstract

The role of adjuvant therapy for renal cell carcinoma (RCC) after surgical resection has been evaluated in numerous randomized and nonrandomized studies using systemic therapies with distinct mechanisms of action. However, adjuvant therapy has not demonstrated definitive benefit to date and guidelines currently do not support its use. Continued advancement in the understanding of the molecular pathogenesis in RCC is critical, which would lead to identification of new therapeutic targets, as well as novel prognostic and predictive biomarkers, in hopes of improving outcomes in this lethal disease. Herein we summarize the results of randomized studies of the adjuvant treatments of RCC, in hopes to direct future effort in the development of treatment of this disease.

Keywords: Kidney cancer; Adjuvant therapy; Nephrectomy; Tyrosine kinase inhibitor; Clinical trials

Introduction

Kidney cancer, which is predominantly renal cell carcinoma (RCC) in histology, is among the most lethal of urologic malignancies. In 2015, a total of 61,560 new cases were estimated to occur in the United States, with approximately 23% expected to die of the disease [1]. Although, the 5-year survival of localized RCC patient is around 90%, this decreases to 65% in patients with locally advanced, nonmetastatic RCC. Despite ongoing effort in clinical testing of adjuvant treatments for those at high risk for recurrence, surveillance remains the standard of care after the curative-intent surgery [2].

The role of adjuvant therapy for RCC after surgical resection has been evaluated in numerous randomized and nonrandomized studies using systemic therapies with distinct mechanisms of action. However, adjuvant therapy has not demonstrated definitive benefit to date [3], and National Comprehensive Cancer Network guideline currently does not support its use [4]. The aim of this review is to summarize the results of randomized studies of in the adjuvant treatment of RCC, in hopes to direct future effort in the development of treatment in this disease.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptor (VEGFR), and other receptor tyrosine kinases, which may be related in part to the anticancer activity of these agents, have been adopted as standard first-line treatment for metastatic RCC [5]. The rapid adoption of these drugs over the prior standard, less effective, and arguably more toxic cytokine therapies, have significantly changed the treatment paradigm for metastatic RCC [6,7]. Fittingly, this has led to the development of several randomized clinical trials evaluating VEGFR TKIs in the adjuvant setting.

Adjuvant sorafenib or sunitinib in unfavorable RCC (ASSURE) is a phase III, double-blinded, multicenter, placebo-controlled trial, designed to evaluate the treatment of either sunitinib or sorafenib, compared with placebo, in patients with advanced RCC (high-grade pT1b–pT2-4, N+) after complete surgical resection [8]. The primary end point

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of the study was disease free survival (DFS), with overall survival and tolerability being secondary end points. The trial was designed to detect 25% reduction in the hazard ratio, corresponding to an improvement from 5.8 to 7.7 years median DFS. Owing to increasing reports of adverse effects leading to patient discontinuations, the treatment doses (sorafenib = 400 mg twice daily or sunitinib = 50 mg once daily) were reduced (sorafenib = 400 mg once daily or sunitinib = 35 mg daily) and then individually titrated thereafter. The results of this trial were initially reported at the 2015 American Society of Clinical Oncology Genitourinary Cancer Symposium, with no survival advantage with TKI adjuvant therapy over placebo for patients with locally advanced RCC. This analysis revealed that treatment with either of the drug resulted in median DFS of 5.6 years, compared to 5.7 years for the placebo arm. Compared with the placebo arm, sunitinib and sorafenib resulted in increased incidence of hypertension (16% and 16% vs. 4%), hand-foot syndrome (33% and 15% vs. $<1\%$), and diarrhea (10% and 9% vs. 0%). Although there are other ongoing randomized studies to evaluate the use of VEGFR TKIs in high-risk RCC, the results of ASSURE are sobering.

Immunotherapy

Before introduction of TKIs, cytokines such as interferon and interleukin were the standard treatment for metastatic RCC. However, trials exploring such therapies in the adjuvant setting failed to demonstrate a clinical benefit. A randomized, multicenter study of adjuvant IFN-α2b vs. observation in patients with completely resected stage II or III RCC, showed no survival advantage compared with placebo [9]. In another phase III study conducted by Eastern Cooperative Oncology Group, 283 patients with pT3–T4a RCC (with or without lymph node involvement) were randomized to 12 cycles of IFN-α-NL or to observation, after surgical resection. With a median follow-up of 10.4 years, compared with observation, this approach also did not improve survival [10].

Overall, 2 studies evaluated the role of immunotherapy consisting of autologous irradiated tumor cells mixed with Bacillus Calmette-Guérin [11] or glycoprotein 96-peptide protein [12], which failed to demonstrate significant benefit in either study. In 2013, Belldegrun and colleagues reported the results of an international, randomized, double blinded, phase III trial of adjuvant RENCAREX. (Girentuximab) vs. placebo, a monoclonal antibody to carbonic anhydrase IX, in 864 patients with locally advanced RCC. With the exception of a subgroup of patients with high expression of carbonic anhydrase IX, no differences in progression-free survival or overall survival were seen [13].

Other approaches

Although incorporation of radiotherapy can be beneficial in the adjuvant treatment of some solid tumors, this approach has failed to show definitive benefit in RCC. In a randomized prospective trial of radiotherapy (50 Gy to tumor bed, ipsi-lateral, and contra-lateral nodes) vs. observation in 72 postnephrectomy patients with stages II to III RCC, there were no differences with regard to relapse rate or survival [14,15]. Another study evaluated the role of hormonal therapy in this setting; Pizzocaro et al. [16] reported in a prospective randomized study of 136 patients who were treated with either medroxypregesterone acetate for 1 year or placebo, and similarly failed to show definitive survival benefit.

Future directions

Despite the disappointing results of adjuvant sunitinib and sorafebib reported in ASSURE, there are currently 2 additional ongoing studies (PROTECT: NCT01235962 and ATLAS: NCT01599754) investigating the role of other VEGFR TKI therapies in the adjuvant setting. PROTECT is a phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety profile of pazopanib as an adjuvant therapy in 1,500 fully resected patients with localized or locally advanced ($\geq$T2), with clear-cell or predominant clear-cell histology RCC. ATLAS is also a phase III, randomized, double-blind, placebo-controlled trial evaluating the effect of axitinib in delaying the recurrence of RCC in approximately 700 patients with localized or locally advanced ($\geq$T2), predominantly clear-cell histology RCC.

Outside of TKI therapy, other adjuvant therapies are also being explored. EVEREST (NCT01120249) is the only phase III trial evaluating the role of mammalian target of rapamycin inhibitor in an adjuvant setting. In this study, high-risk patients (high-grade pT1bN0M0 or pT2-4N+M0) within 84 days from a complete resection are randomized to either everolimus or placebo for a period of 1 year. Additionally, emerging data in treatment of metastatic RCC using immune checkpoint inhibitors have led to new clinical trials investigating its role in earlier disease. One such ongoing study is a phase 2 study of MPDL3280A (an anti–programmed death ligand 1antibody) as monotherapy or in combination with bevacizumab compared with sunitinib in patients with untreated advanced and metastatic RCC. The results of these ongoing studies are highly anticipated and it would be interesting to see if they would demonstrate any survival advantages and whether their toxicity profiles would be different.

Prognostic models: Phenotype vs. molecular

Understanding which patients are at risk for relapse after local therapy is paramount when designing an adjuvant trial. To estimate the risk of disease recurrence for RCC, initial models and nomograms were predominantly based clinical parameters such as TNM stage, nuclear grade, microvascular invasion, tumor necrosis, and performance status [2,17–20],