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Review Article

Recent advances in localized RCC: A focus on VEGF and immuno-oncology therapies

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Abstract

Recent advances in advanced renal cell cancer (RCC) research have produced new drugs and therapies for patients with metastatic disease leading to higher response rates, improvements in progression-free survival, and longer overall survival. These advances have yet to be realized in patients with early-stage kidney cancer, and to date, no drug has been approved for the adjuvant treatment of localized kidney cancer. The current standard of care for localized high-risk kidney cancers is resection of the primary tumor. Here, we review the results of recently completed adjuvant vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase inhibitor (TKI) trials in RCC that have been reported, or are awaiting results. Further, we discuss the new immune checkpoint inhibitor adjuvant trials planned. There is hope that these trials may lead to new options and longer survival for patients with localized high-risk kidney cancer.

Keywords: Renal cell carcinoma; Nephrectomy; VEGF-targeted therapy, ASSURE, S-TRAC, Immunotherapy

1. Introduction

In the decade spanning 2006 to 2016, 10 drugs targeting angiogenesis were approved for the treatment of metastatic RCC, based on the recognition that inactivation of von Hippel Lindau (VHL) pathway was a dominant driver of clear cell RCC [1]. Sequential use of these new agents led to an improvement in response rates, progression-free survival, and improvement in overall survival (OS), offering multiple treatment options for patients. These drugs include the VEGF-TKI inhibitors (sorafenib, sunitinib, pazopanib, and axitinib), the VEGF antibody bevacizumab, and mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus). Recently, the VEGF-TKIs, cabozantinib, and lenvatinib (in combination with everolimus), were approved based on improvement in the primary endpoint of PFS, while the immune checkpoint inhibitor, nivolumab, was approved for advanced RCC when it demonstrated an improvement in OS [2]. Activity of these agents in metastatic renal cancer has led investigators to postulate that their use in earlier stage of disease might prevent or delay the occurrence of metastases. The current standard of care for localized kidney cancer is resection of the primary tumor. Since in many patients it will recur after their tumor is resected, various nomograms have been used to predict tumor recurrence and survival. One such nomogram predicts 5-year survival with low-risk kidney cancer to be 92%, intermediate-risk disease to be 67%, and high-risk disease to be 44 % with resection alone [3]. Based on the effect that VEGF-TKIs had on metastatic disease, adjuvant trials with these agents were initiated in 2006, and several have now reached their primary endpoints. Positive results could lead to major changes to the management of localized kidney cancer.

2. Older contemporary immunotherapy trials

Older adjuvant phase III studies for mRCC largely involved immunotherapeutic agents such as interferon-α (IFN-α) or interleukin-2 (IL-2). The following summary highlights these earlier cytokine-based immunotherapies.

The Eastern Cooperative Oncology Group conducted a randomized trial of IFN-α ($n = 283$) vs. observation for 6 months in patients who either had pT3-4aN0M0 or

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pTxN1-3M0 disease with the primary endpoint of improving 5-year OS. Patients were allowed to have dosing of IFN-α for 5 days every 3 weeks, with a starting dose of 3 MIU on day 1, 5 MIU on day 2, and escalation up to 20 MIU on days 3 to 5. The 5-year OS underperformed in the treatment arm with 51% vs. 62% in the observation arm ($P = 0.9$), and there was no difference in recurrence-free survival [4].

In another trial, 247 patients with resected pT3a-bN0M0 or pT2/3N1M0 disease received either observation or 6 million international units of IFN-a 3 times/week for 6 months. The trial demonstrated a 5-year DFS of 67.1% in the treatment arm and 56.7% in the control arm, and no difference in 5-year OS [5].

A high-dose IL-2 trial conducted by the Cytokine Working Group in patients with both locally advanced (either pT3b-4Nx or pTxN1-3 disease) and completely resected metastatic disease randomized patients to 1 course of IL-2 (600,000 U/kg every 8 hours on days 1–5 and days 15 to 19 [maximum 28 doses]) or to observation, with a projected improvement in 2-year DFS from 40% to 70%. However, the study was closed early when no difference in OS was seen [6].

The Adjuvant Rencarex Immunotherapy Phase III Trial to Study Efficacy in nonmetastatic RCC (ARISER) evaluated a chimeric monoclonal antibody, cG250, that binds to the carbonic anhydrase 9 (CAIX) antigen (present in 95% of ccRCC), vs. placebo control ($n = 864$) with DFS as a primary endpoint and OS as secondary endpoint after nephrectomy. Eligible adult patients (pT1b/pT2 high-grade-PTanyN+M0) had undergone a nephrectomy for ccRCC. Patients received either a single loading dose of girentuximab, 50 mg (week 1), followed by weekly intravenous infusions of girentuximab, 20 mg (weeks 2–24), or placebo. The 5-year DFS was 53.9% for girentuximab and 51.6% for placebo with no statistically significant difference in DFS ($P = 0.74$) or OS ($P = 0.94$). Exploratory subgroup analyses showed a nonsignificant girentuximab treatment benefit of improved DFS with increasing CAIX score. In the subgroup of patients with CAIX score of 200 or greater ($n = 392$), treatment of girentuximab was associated with a nonsignificant improved DFS (HR = 0.75; 95% CI: 0.55–1.04; $P = .08$), including patients younger than 65 years, patients with ECOG status of 0, and patients with G1/G2 tumors [7,8].

A novel approach in the adjuvant therapy setting used heat shock protein peptide complex (Vitespen) that works by increasing NK cell response and advancing the CD8 T-cell immune response. One trial randomized 818 patients with high-risk localized RCC to Vitespen or placebo [9]. The median follow-up was 2 years, and no difference in DFS was seen. Vitespen showed an insignificant reduction in disease recurrence ($P = 0.506$, 37.7% in Vitespen group vs. 39.8 % in placebo group).

In a vaccine trial done in Germany, 558 patients were randomized to 6 intradermal injections of adjuvant vaccine generated from primary tumor vs. no treatment which was administered to patients with pT2-3bN0-3M0 renal cell cancer. A total of 379 patients were evaluable for the primary endpoint of DFS, with a positive result. With 5 years of follow-up, the HR for tumor progression was 1.58 (95% CI: 1.05–2.37, $P = .02$), favoring the vaccine group. However, there was an imbalance in stratification arms, and 76% of patients on the vaccine arm had clear cell histology, as opposed to 68% of patients on the control arm, which may have contributed to this result [10].

In summary, past studies of cytokine-based immunotherapy administered in the adjuvant setting have not demonstrated the benefit of immunotherapy; however, these cytokine-based agents such as Interferon and IL-2 may not be able to adequately prime the immune system in the absence of tumor. As will be discussed later, the use of immunotherapy in the adjuvant RCC setting has recently generated new clinical trial interest [11].

3. Rationale for antiangiogenic therapy and current VEGF trials

The sequential use of VEGF-targeted therapy improved median OS from 13 months to >24 months in advanced disease [12]; this prompted the evaluation of these agents in multiple adjuvant trials. Six small-molecule antiangiogenic targeted trials have completed accrual and have reported results or are maturing: ASSURE, S-TRAC, SORCE, PROTECT, ATLAS, and EVEREST.

3.1. VEGF and mRCC

ASSURE, Adjuvant Sorafenib or Sunitinib in Unfavorable Resected REnal cancer (E2805) [13] was the largest randomized placebo-controlled trial conducted in RCC and included 1943 patients with T1b high-gradeN0M0 to TanyN+M0 disease and was powered to clear cell but allowed enrollment of non-clear-cell histology based on UCLA International staging criteria (UISS) [1]. Patients were randomized after partial or radical nephrectomy to receive sunitinib ($n = 647$), sorafenib ($n = 649$), or placebo ($n = 647$) for 1 year. Surgical approach (robotic or open), histology, modified UISS prognostic group high or intermediate risk, and ECOG performance score were the stratification factors. ASSURE was designed to evaluate sunitinib 50 mg on a 4/2 schedule, sorafenib 800 mg daily continuously, or equivalent placebo. However, after 1,300 patients were enrolled, the starting doses were lowered, due to higher than expected attrition from intolerance or toxicity to 37.5 mg for sunitinib and 400 mg daily for sorafenib for the first 1 to 2 cycles with mandatory dose escalation if tolerated. The primary endpoint of the trial was to compare DFS between each experimental arm and placebo. DFS by clear cell histology, overall survival, and toxicity were secondary endpoints. The primary analysis showed no significant differences in DFS for sunitinib (5.8 years;