Review

Adjuvant Therapy for Renal Cell Carcinoma

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Abstract

In the past few years, several targeted therapies have been approved by the U.S. Food and Drug Administration for the treatment of advanced renal cell carcinoma. This has led to an improvement in the progression-free survival and quality of life for these patients. Nevertheless, the use of these and other therapies in the adjuvant setting has failed to demonstrate a clear benefit. Immune therapies and hormonal or targeted therapies have been studied in this indication, and there are clinical trials currently enrolling patients with high risk of relapse. This article reviews the available data and the ongoing trials exploring the role of adjuvant therapy for kidney cancer.

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Introduction

Renal cell carcinoma (RCC), according to data from Global Burden of Cancer Study 2008, has an annual incidence of more than 270,000 new cases globally, with a male:female ratio of 1.6:1; worldwide, RCC accounted for 116,000 deaths.[1] Because of a wider use of imaging diagnostic procedures, there has been a stage and size migration, allowing the detection of more tumors in an earlier stage of the disease; nowadays, the detection of asymptomatic renal masses accounts for approximately 50% of all renal tumors discovered.[2]

The incidence of RCC is increasing continually in recent decades, and approximately two-thirds of the cases are diagnosed without evidence of metastatic disease. These patients are usually managed with a radical surgical approach, but a percentage of patients will have recurrence and eventually die because of the disease. Estimated 5-year survival of localized RCC patients is approximately 90%, decreasing to 65% in locally advanced RCC, and only 12% in metastatic RCC.[3]

Therefore, relapse risk reduction through appropriate adjuvant treatment could be of great help in patients at a higher risk of relapse, but up to now no agent has proven to be useful in this setting. Immune therapies, hormonal therapies, and finally targeted therapy, effective in the advanced setting, have been tested for this indication, without success to date. In this article, we will review the completed adjuvant trials and the ongoing ones, and future research possibilities for this unmet medical need.

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Risk Stratification

When considering adjuvant therapy, it is very important to select the patients who are at a higher risk of relapse, because these will be the ones more likely to have any benefit from the treatment. As stated, patients with no evidence of metastatic disease at diagnosis might have a risk of relapse up to 35% or 40%; but if we treat every patient with early-stage RCC, we would be causing an excess of toxicity without any proven benefit.

For patients with a partial or radical nephrectomy, the risk of recurrence largely depends on tumor size, grade, stage, histology, performance status, and completeness of resection.[4,5] Currently, pathologic tumor stage is the single most important prognostic factor in resected RCC, but does not fully explain disparities in survival among stages.[6] Some other histologic features, such as Fuhrman grade, histologic subtype, and presence of necrosis or sarcomatoid component have been linked with a poorer prognosis.[7] Regarding histologic subtypes, chromophobe and papillary type I seem to have a more indolent clinical course, and papillary type II and clear-cell RCC show a more aggressive behavior.[8] Molecular biology strategies, testing carbonic anhydrase IX (CA-IX), vimentin, Ki-67, p53, or phosphatase and tensin homolog, although having shown a potential role for predicting recurrence risk,[9] are not routinely used in clinical practice.

Nomograms have been developed to estimate the recurrence of risk and survival of RCC patients. The first one designed to predict freedom from recurrence was developed by the Memorial Sloan-Kettering Cancer Center, and it included pathologic tumor stage, tumor size, histologic subtype, and symptoms at the time of presentation[10]; this model was able to predict recurrence with an area under the curve (AUC) of 0.74. It was updated in 2005, using stage, tumor size, necrosis, vascular invasion, Fuhrman grade, and clinical symptoms, with an improved AUC of 0.82.[11] The Leibovich score or Stage, Size, Grade, and Necrosis (SSIGN) score, developed at the

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Mayo Clinic, included stage, size, grade, and necrosis, classifying patients into low, intermediate, or high risk of relapse, with an AUC of 0.84[12]; this score was externally validated in an independent study, confirming its high accuracy, with an AUC of 0.88.[13] The score from the University of California Los Angeles, named Integrated Staging System (UISS), predicts overall survival (OS) of RCC patients based on stage, Fuhrman grade, and performance status, and is validated for localized and metastatic RCC.[14] These nomograms have been used in some of the trials that will be reviewed herein to stratify patients into risk categories.

Completed Adjuvant Trials

A systematic review with meta-analysis of adjuvant therapies for locally advanced renal cell cancer was published in 2011[15]; it concluded that there was no support for using systemic therapy in the adjuvant setting, because there was no evidence of any benefit, and it caused substantial toxicity. The therapeutic modalities included in this study were mainly chemotherapy, immune therapies, and hormonal treatments, because no trial with targeted therapies was completed at that time. There are some completed clinical trials that are worth reviewing.

Immune Therapy Trials

Immunotherapy was one of the standard options for metastatic RCC before the advent of targeted therapies. Interleukin (IL)-2 and interferon (IFN) were commonly used in that setting, but with poor results, achieving a response rate of 6% to 10% and some durable responses, and a median OS of 12 to 15 months.[16] Nevertheless, none of the adjuvant trials with immune therapies have been successful. Two trials compared IFN with placebo in T3 to T4 and/or node-positive patients, without improvements in disease-free survival (DFS) or OS.[17,18] Two other small trials that explored the role of IL-2, whether in monotherapy as a single-dose treatment[19] or combined with IFN,[20] also had negative results. A triple combination of IL-2, IFN, and 5-fluorouracil also failed to show an improvement in DFS compared with placebo, and was associated with significant toxicity.[21] This same schedule was tested in a different trial, showing no differences in DFS, but a worse OS for the treatment arm.[22]

Some other trials have explored the potential role in the adjuvant setting of therapeutic vaccines. One study using autologous irradiated tumor cells mixed with bacillus Calmette-Guérin did not show any benefit in DFS[23]; similarly, results of another trial with autologous tumor-derived heat-shock protein (glycoprotein 96)-peptide complex were also negative.[24] The only adjuvant trial with this approach to show a significant benefit in DFS used an autologous RCC lysate vaccine, but the high number of patients lost after randomization (32%), the imbalance of this loss between treatment arms, and the absence of OS data led to criticism of the results[25]; however, a recent update of the results with 10-year follow up did reveal a benefit in OS, mainly in pT3 patients.[26]

Finally, a trial that has recently reported first results is the Adjuvant RENCAREX® Immunotherapy trial to Study Efficacy in non-metastasised Renal cell carcinoma trial with girentuximab, a monoclonal antibody that binds the CA-IX cell surface antigen, present in 95% of RCC. This international, randomized, double-blind phase III trial compared girentuximab with placebo, and enrolled 864 high-risk patients. There were no differences in progression-free survival (PFS) or OS between arms. Nevertheless, in a subgroup analysis, patients with high expression of CA-IX who received girentuximab had better PFS than those given placebo (hazard ratio, 0.55; $P = .01$).[27]

Other Treatment Modalities

The use of radiotherapy in an adjuvant setting has not been established as a standard for this indication. In a trial published in 1987, a total of 72 patients with stage II to III kidney cancer were randomized to adjuvant radiation therapy (50 Gy in the tumor bed and both ipsilateral and contralateral nodes) or no further treatment. This trail was closed early because of unacceptable toxicity, and no differences in relapse rate or survival were seen between both arms.[28] A similar trial performed even earlier, in the 1970s, also did not find a benefit from postoperative radiation therapy.[29]

Some other studies explored the role of hormone therapies, with disappointing results. One prospective multicenter study compared medroxyprogesterone acetate treatment for 1 year versus no treatment after radical nephrectomy, and failed to demonstrate any benefit in survival.[30] Another trial testing chemotherapy with adjuvant UFT (tegafur and uracil) was also unsuccessful.[31]

Therefore, no treatment has demonstrated substantial and consistent benefit in the adjuvant setting for renal cell carcinoma, whether using immunotherapy, radiotherapy, hormonal therapy, or chemotherapy. Trials testing targeted therapies will be reviewed in the next section, because none of them have published final results and are still ongoing, some of them still accruing patients, and some others closed and with results pending.

Ongoing Adjuvant Trials

Targeted therapy has changed the therapeutic scenario and the clinical course of patients with advanced RCC in the past few years. These agents are already approved for their use in the setting of advanced RCC, and some of them are currently being explored with an adjuvant intent (Figure 1). The rationale for most of these trials is similar to that seen in various tumor types: those treatments that have proven to be highly effective in the advanced setting may be tested in an adjuvant indication.

Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer Trial

This phase III randomized, double-blind, placebo-controlled trial recruited more than 1600 patients with intermediate or high risk of relapse according to SSIGN criteria. It compares placebo with sorafenib for 1 year or 3 years of adjuvant therapy, with DFS as a primary end point (NCT00492258). This trial recently presented data regarding patients' clinical characteristics and surgical approaches,[32] but efficacy analysis will not be ready until 2016.

Sunitinib Treatment of Renal Adjuvant Cancer Trial

This phase III randomized, double-blind, placebo-controlled trial, with 500 patients included fulfilling high-risk criteria (UISS), is testing sunitinib for 1 year as adjuvant therapy. The primary end point is DFS, and results are expected through 2017 (NCT00375674).