Systemic adjuvant therapies in renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) is one of the ten most frequent solid tumors worldwide. Recent innovations in the treatment of metastatic disease have led to new therapeutic approaches being investigated in the adjuvant setting. Observation is the only current standard of care after radical nephrectomy, although there is evidence of efficacy of adjuvant use of vaccine among all the strategies used. This article aims to collect published experiences with systemic adjuvant approaches in RCC and to describe the results of past and ongoing phase III clinical trials in this field. We explored all the systemic treatments, including chemotherapy, immunotherapy and targeted drugs while alternative approaches have also been described. Appropriate selection of patients who would benefit from adjuvant therapies remains a crucial dilemma. Although the international guidelines do not actually recommend any adjuvant treatment after radical surgery for RCC, no conclusions have yet been drawn pending the results of the promising ongoing clinical trials with the target therapies. The significant changes that these new drugs have made on advanced disease outcome could represent the key to innovation in terms of preventing recurrence, delaying relapse and prolonging survival after radical surgery for RCC.

Introduction

Renal cell carcinoma (RCC) is the ninth most common cancer in women and the seventh in men. It is responsible for 2.3% of all malignant cancers in adults. The RCC incidence worldwide is 209,000 new cases and 102,000 deaths each year.1,2 Incidence rates have almost doubled over the past 30 years from 7.1 per 100,000 in 1975 to an age-adjusted incidence rate of 14.6 per 100,000 men and women per year in 2004-2008. The age-adjusted death rate was 4.0 per 100,000 men and women per year in the United States in 2004-2008.2,4 The disease is predominant in men and usually occurs during the sixth or seventh decade of life. The best known risk factors are tobacco smoking, obesity and hypertension; also occupational risks have been evidenced, such as exposure to steel, iron, asbestos, cadmium and petroleum. Finally, genetic conditions such as Von Hippel Lindau syndrome, hereditary papillary renal carcinoma and Birt-Hogg-Dubé syndrome are forms of inherited RCC.4,6

The American Joint Committee on Cancer (AJCC) describes five subtypes of RCC: conventional (clear cell), papillary, chromophobe, collecting duct and unclassified.7 Clear cell carcinoma represents about 80% of RCCs and is the most used in clinical trials as a pattern for therapy and prognosis.

The main therapeutic approach in early RCC is surgery, with radical or partial nephrectomy. Recent years have seen both these techniques evolve and they can now be performed safely by laparoscopy.8,10 For smaller tumors, the nephron sparing technique should always be considered. Partial nephrectomy has been proven to be as effective as radical nephrectomy in carefully selected cases.11,12

The strongest indicator of prognosis in RCC is stage at diagnosis. Using 2010 TNM staging criteria, the reported 5-year survival rates range from 81% in stage I to 8% in stage IV.13

Approximately 30% of patients with RCC have metastatic disease at presentation and there is disease recurrence in approximately 40% of patients initially treated for a localized disease.14 The median time to relapse after nephrectomy is 15–18 months, and 85% of relapses occur within three years.15

Several factors are associated with a worse prognosis after radical nephrectomy and correlate strongly with survival: regional lymph node involvement,16 histological features (Fuhrman nuclear grading, presence of necrosis, microvascular invasion, sarcomatoid, papillary or chromophobe features),17-23 stage and nuclear grade,22 tumor size,24 Variables related to the patient also influence prognosis: a low performance status, the presence of symptoms at the moment of diagnosis, cachexia and alterations in some laboratory parameters are related to a worse prognosis.16 Finally, some molecular markers have demonstrated a prognostic value in RCC: a low expression of the transmembrane carbonic anhydrase IX (CAIX),25-29 elevated serum vascular endothelial growth factor (VEGF) levels30 and other biomarkers whose weight and role are still to be defined.25,31

The recent discovery of new prognostic factors led to the develop-
ment of prognostic nomograms and algorithms that are very useful for stratifying patient risk of relapse. Among the best known of these models is the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram, including pathological stage, Fuhrman nuclear grading, tumor size, necrosis, vascular invasion and clinical presentation,22 the University of California Los Angeles Integrated Staging System (UISS), based on Eastern Cooperative Oncology Group (ECOG) performance status, Fuhrman nuclear grading and pathological stage according to the 2002 TNM staging system,23 the Mayo Clinic Stage Size Grade and Necrosis (SSIGN) score, that takes into consideration TNM stage, tumor size, nuclear grade and histological tumor necrosis,24 the Karakiewicz nomogram, based on TNM stage, Fuhrman grade, histological subtype, local symptoms, age, and sex,25 the Leibovich score, including tumor stage, regional lymph node status, tumor size, nuclear grade, histological tumor necrosis and with the recent addition of scoring for vascular invasion, with a higher predictive accuracy.26-28 Several comparative studies have been performed to assess the best predictive value among all these different nomograms. Two retrospective studies comparing SSIGN and Leibovich scores with UISS score suggested that the SSIGN and Leibovich scores offer a better stratification for clear cell RCC than the UISS model.29,30 More recently, the Karakiewicz nomogram emerged as a better clinical predictor for survival outcomes in patients with localized disease when compared to the Leibovich model.31,32 The risk stratification offered by these nomograms for individual patients is necessary in order to develop tailored treatments that could reduce the risk of relapse and enhance the chance of successful disease management; in the context of adjuvant treatment, these algorithms are useful to better select which patients should be enrolled in ongoing clinical trials with new molecules.

Regarding the current standard of care after radical surgery, the most recent National Comprehensive Cancer Network (NCCN) Guidelines for kidney cancer declared that adjuvant treatment currently has no established role. This was based on the absence of any systemic therapy capable of reducing the likelihood of relapse.33 For the moment, observation remains the standard of care after nephrectomy, with the possibility of enrollment in randomized clinical trials reserved only for eligible patients. A meta-analysis of ten studies on various systemic adjuvant therapy in RCC was recently performed by Scher et al.34 The authors examined randomized controlled trials and compared adjuvant therapy versus observation after surgery. They analyzed the outcome as overall survival (OS), disease free survival (DFS) and severe toxicities. Different strategies of treatment were evaluated separately: subgroup analysis among immunotherapy, hormone therapy, biochemotherapy and vaccines showed no relevant results. The adjuvant therapy provided no benefits in terms of OS (HR=1.07, 95% CI 0.89-1.28; P=0.48; no heterogeneity) or DFS (HR=1.03, 95% CI 0.87-1.21, P=0.77; heterogeneity measured as I²=40%) when compared with no treatment. Evaluation of toxicity showed a higher incidence of adverse events in the adjuvant therapy groups.35 Development of an adjuvant therapy requires an evidence-based approach and an in-depth knowledge of the molecular basis of the disease. An effective adjuvant drug for RCC should be relatively non-toxic, have established efficacy in the metastatic setting (with the exception of immunotherapy, which was shown to be more effective for residual and indolent disease) and have demonstrated efficacy against the standard of care in randomized trials. A gain in OS should be considered as criteria for efficacy of adjuvant treatment. Furthermore, the appropriate identification of patients at the highest risk of relapse, or who are more sensitive to particular drugs as potential beneficiaries of this treatment approach, is a crucial question in the adjuvant setting. Indeed, our ability to predict relapse has much room for improvement. Finally, we should consider that patients with low risk of recurrence are not ideal candidates for adjuvant treatment.

### Methods of research

The purpose of the present study is to review the most up-to-date literature in systemic adjuvant treatment for RCC after radical surgery; phase III randomized trials have been included. Publications on adjuvant therapy for RCC were obtained from the PubMed database using the subsequent MeSH (Medical Subject Heading) terms: CHEMOTHERAPY and IMMUNOTHERAPY and CANCER VACCINES and ADJUVANT, each combined with CARCINOMA, RENAL CELL. We also used combinations of the following words: KIDNEY CANCER and POST-OPERATIVE TREATMENT and CHEMOTHERAPY and IMMUNOTHERAPY and VACCINES and ADJUVANT THERAPY and RANDOMIZED CONTROLLED TRIALS. The ongoing randomized phase III clinical trials were obtained on the official website (www.clinicaltrials.gov). The search was completed by exploring the abstract databases from the most important international scientific meetings.

### Adjuvant immunotherapy

Immunotherapy for RCC has been available for the past 30 years: the ability of renal cancer to evoke an immune response led to the use of immunotherapy for patients with metastatic RCC. Different strategies have been explored in an attempt to reproduce and to improve the natural immune response. The most consistent results have been reported both with the vaccines and with cytokines [interleukin-2 (IL-2) and interferon-alpha (IFN-α)], used alone or in combination. The cytokines increased both the activity of cytotoxic lymphocytes and of natural killer (NK) cells, modulating, as vaccines, the host immune system response to tumor cells.36-38 Several randomized trials have been performed to assess the efficacy of immunotherapy in the adjuvant setting (Table 1),39-44 but most have failed to show any survival advantage.

IFN-α modulates cell growth and function, directly inhibiting cell proliferation and regulating the antigenic differentiation and expression of the cell. It is one of the active drugs in metastatic disease and has been shown to improve survival in metastatic RCC patients.44,45-50

### Table 1. Adjuvant immunotherapy trials in renal cell cancer.

<table>
<thead>
<tr>
<th>Author et al., 2001</th>
<th>No. patients</th>
<th>Stage</th>
<th>Treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizzocaro et al., 2001</td>
<td>245</td>
<td>Robson II-III</td>
<td>IFN-α-2b</td>
<td>OS</td>
<td>No difference in DFS or OS</td>
</tr>
<tr>
<td>Messing et al., 2003</td>
<td>238</td>
<td>pT3b-4, pN1-3, resected</td>
<td>IL-2</td>
<td>DFS</td>
<td>No difference in DFS or OS</td>
</tr>
<tr>
<td>Pasalacqua et al., 2007</td>
<td>310</td>
<td>pT1 over 2.5 cm, pT2-3, pN0-3</td>
<td>IL-2+IFN-α</td>
<td>OS</td>
<td>No difference in DFS or OS</td>
</tr>
</tbody>
</table>

**Table 1. Adjuvant immunotherapy trials in renal cell cancer.**
feasible, did not produce the ambitious clinically meaningful benefit anticipated when administered postoperatively to patients with resected high-risk RCC.46

The combination of IL-2 and IFN-α with adjuvant purpose for RCC has also been explored. A multicenter randomized Group Oncologico Italiano di Ricerca Clinica (GOIRC) study, comparing the combination of subcutaneous low-dose IL-2 plus IFN-α versus observation, was presented at the 2007 American Society of Clinical Oncology (ASCO) annual meeting.47 The peculiarities of this study are the long duration of immunotherapy treatment, with courses repeated for four weeks every 4-6 months up to five years after surgery, and the inclusion of patients with low risk of relapse, i.e. pT1 or N0 tumors. The trial enrolled 310 patients; intention-to-treat analysis at a median follow up of 52 months showed no significant differences between patients and controls. In the first five years of observation, RFS curves were similar in the two arms, but thereafter diverged. The actuarial RFS at five and ten years was, respectively, 73% and 73% in treated patients and 73% and 60% in controls (HR 0.84, 95% CI 0.54-1.33, P=0.47). Efficacy of immunotherapy was more evident in patients with good PS (HR 0.78, 95% CI 0.47-1.30, P=0.35), age under 60 years (HR 0.61, 95% CI 0.31-1.19, P=0.15), and low tumor grade (HR 0.70, 95% CI 0.38-1.27, P=0.24). No differences in OS between the two arms were observed. Toxicity was mild in the majority of cases.48

Innovation in adjuvant immunotherapy: the vaccines

Vaccines with antigens derived from tumor cells have been used in an attempt to stimulate the specific immune response against the tumor both in the adjuvant and the metastatic setting for RCC (Table 2).55,57 Several vaccines have been tested as adjuvant therapy, including tumor cell lysates and irradiated and cryopreserved preparations of tumor cells.58

In 1996, in one of the first studies performed, Galligioni et al. randomized 120 patients undergoing nephrectomy for RCC to receive intradermal injections of irradiated autologous tumor cells alone or mixed with Bacillus of Calmette and Guerin versus observation. The treated patients were evaluated for the development of delayed type cutaneous hypersensitivity (DTCH) response to autologous tumor and autologous normal renal cells. After a median follow up of 61 months, there were no differences in OS and in rate of relapse between patients who received adjuvant therapy and controls.55 The data obtained clearly indicate that active specific immunotherapy can increase the reactivity to autologous tumor, as measured by the DTCH test, but it appears unable to affect either DFS or OS. More recently, Jocham et al. conducted a multicenter phase III randomized controlled trial using six month-

Table 2. Adjuvant vaccines trials in renal cell cancer.

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Stage</th>
<th>Treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galligioni et al., 199655</td>
<td>pT1-3, pN1-3</td>
<td>Intradermal vaccination with BCG mixed with irradiated cells</td>
<td>DTCH response</td>
<td>Significant DTCH response to autologous tumor No difference in DFS No difference in OS</td>
</tr>
<tr>
<td>Jocham et al., 200456</td>
<td>pT2-3b, pN0-3</td>
<td>Autologous vaccine (Reniace®)</td>
<td>PFS</td>
<td>Improvement in the 5-year DFS No difference in OS</td>
</tr>
<tr>
<td>Wood et al., 200857</td>
<td>T1b-4, N1-3</td>
<td>Vitespen®6*</td>
<td>RFS</td>
<td>No difference in RFS</td>
</tr>
</tbody>
</table>

BCG, Bacillus Calmette-Guérin; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival (including both disease relapse or death); DTCH, delayed type cutaneous hypersensitivity. *An autologous, tumor-derived heat-shock protein glycoprotein 96–peptide complex.
ly injections of individually prepared autologous renal tumor cell vaccin- 
y as adjuvant treatment for patients undergoing radical nephrecto-
my. The primary end point of the trial was the reduction of the risk of 
tumor progression, defined as relapse or death (PFS for the authors). This 
autologous vaccine was well tolerated and showed a statistically 
significant benefit when compared with observation. To our knowledge, 
this is the only adjuvant trial in RCC to date that shows a potential PFS 
advantage. A total of 379 patients with stage pT2-3b RCC, with or with- 
out lymph node involvement and without distant metastasis, were 
included in the analysis. At 5-year and 7-month follow-ups, the hazard 
ratios for tumor progression were 1.58 (95% CI 1.05-2.37) and 1.59 
(1.07-2.36), respectively, in favor of the vaccine group (P=0.02, log rank 
test); 5-year and 7-month PFS rates were 77.4% and 72% in the vac-
 
Table 3. Adjuvant chemotherapy and chemoimmunotherapy trials in renal cell cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Stage</th>
<th>Treatment</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masuda et al., 1992</td>
<td>31</td>
<td>Stage I, II or III</td>
<td>VNBL+ Doxo+ UFT</td>
<td>OS</td>
<td>Improvement in 5-year OS</td>
</tr>
<tr>
<td>Atzpodien et al., 2005</td>
<td>203</td>
<td>pT3b/c-T4, N1-3, resected MI</td>
<td>IL-2+IFN-α+ 2a+5-FU</td>
<td>OS</td>
<td>Detrimental in OS</td>
</tr>
<tr>
<td>Aitchison et al., 2011</td>
<td>309</td>
<td>High risk patients and 5-fluorouracil</td>
<td>IL-2+IFN-α+ UFT</td>
<td>No difference in OS</td>
<td>No difference in DFS</td>
</tr>
</tbody>
</table>

Note: VNBL, vinblastine; Doxo, doxorubicin; UFT, tegafur-uracil; OS, overall survival; DFS, disease-free survival.
year, following radical nephrectomy for M0 renal cancer.\textsuperscript{59} The study, including patients with any T stage and also patients with lymph node involvement, randomized 136 patients to receive MPA 500 mg orally three times per week \textit{versus} observation. At a median follow up of three years, 26\% of patients in the treatment arm had a recurrence, compared with 24\% of patients in the control arm; recurrence was more frequent in tumors without estrogen receptors. Treatment was associated with significant systemic toxicity without any benefit; the hormonal strategy was, therefore, completely abandoned after this first approach.

More recently, thalidomide has also been evaluated in 46 patients in a randomized phase III trial conducted by the MD Anderson Cancer Center. After a median follow up of 43.9 months, patients on the thalidomide arm had inferior 2- and 3-year probabilities of RFS compared with controls (47.8\% \textit{vs} 69.3\% and 28.7\% \textit{vs} 69.3\%, respectively; P=0.022); the cancer-specific survival was similar for both groups. In conclusion, postoperative treatment with thalidomide for high-risk RCC is detrimental to RFS rates and did not improve cancer-specific death rates.\textsuperscript{79}

### Ongoing trials into targeted therapy in an adjuvant setting

The inhibition of angiogenesis using targeted therapies is a promising strategy in most solid tumors and appears to be particularly attractive in RCC. At present, three classes of drugs with antiangiogenic activity have been approved and extensively studied for this tumor: circulating VEGF inhibitors, such as bevacizumab; multi-targeted receptor tyrosine-kinase inhibitors (TKIs) of VEGFR, such as sorafenib, sunitinib, pazopanib and axitinib; inhibitors of mammalian target of rapamycin (mTOR) related to protein synthesis and to angiogenesis, such as temsirolimus and everolimus.\textsuperscript{14,71-76}

The next logical step would be to test them in the adjuvant setting and several studies are currently ongoing to assess this possibility. On the other hand, a potential negative effect of anti-VEGF drugs when used for this purpose has been suggested since some studies proved an alteration in the host microenvironment that may facilitate the development of metastases.\textsuperscript{77} Other pre-clinical evidence seems to indicate that while TKIs can reduce primary tumor growth, they can also promote tumor invasiveness and metastasis.\textsuperscript{78,79} For these reasons, which, however, have yet to be assessed, targeted agents in the adjuvant setting should only be administered in the context of a clinical trial.

No article concerning the new targeted drugs has been published so far, but several phase III adjuvant trials on RCC are currently underway with sorafenib, sunitinib, everolimus and pazopanib (Table 4).\textsuperscript{80-90} At present, the use of inhibitors of tyrosine kinase of VEGFR should only be considered in high-risk patients. Further studies are needed to clarify the role of targeted therapies in the adjuvant setting as well as in the postoperatively setting.

Table 4. Phase III ongoing trials in adjuvant renal cell cancer.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Histology</th>
<th>Risk/stage</th>
<th>Trial design</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE\textsuperscript{81}</td>
<td>All</td>
<td>pT1b G3-4, pT2-4, N+</td>
<td>Sorafenib \textit{vs} sunitinib \textit{vs} placebo</td>
</tr>
<tr>
<td>SORCE\textsuperscript{81}</td>
<td>All</td>
<td>High and intermediate risk</td>
<td>1-year sorafenib \textit{vs} 3-year sorafenib \textit{vs} placebo</td>
</tr>
<tr>
<td>S-TRAC\textsuperscript{82}</td>
<td>Predominant clear cell</td>
<td>High risk (UISS criteria)</td>
<td>Sunitinib \textit{vs} placebo</td>
</tr>
<tr>
<td>ARISER\textsuperscript{83-86}</td>
<td>Clear cell</td>
<td>T1b or T2, N0/NX, M0, each with G3, or T3a/b/c, or T4 N0/NX, M0, or any T stage and N+M0</td>
<td>Monoclonal chimeric antibody G250 \textit{vs} placebo</td>
</tr>
<tr>
<td>EVEREST\textsuperscript{87,88}</td>
<td>All</td>
<td>Intermediate high risk or very high risk</td>
<td>Everolimus \textit{vs} placebo</td>
</tr>
<tr>
<td>PROTECT\textsuperscript{89,90}</td>
<td>Clear-cell or predominant clear-cell</td>
<td>pT2, G3 or G4, N0; or pT3, G any, N0; or pT4, G any, N0; or pT any, G any, N1</td>
<td>Pazopanib \textit{vs} placebo</td>
</tr>
</tbody>
</table>

UISS, University of California Los Angeles Integrated Staging System.

### Conclusions

The recent innovations in the treatment of metastatic RCC, with the setting of new standards and the improvement in OS to over 17 months,\textsuperscript{91} has suggested the usefulness of investigating these same strategies in the adjuvant setting in the hope that the progress seen in metastatic disease trials will also be made in this context.

Up to now, only an autologous vaccine has shown some benefit among all the systemic therapies tested so far in the adjuvant setting.\textsuperscript{86,88} and some subgroups of patients at low risk could benefit from low doses of IL-2 and IFN-\(\alpha\).\textsuperscript{48} These few data, although significant, require further validation and have yet to change the standard after radical nephrectomy, since the actual standard of care after radical nephrectomy for M0 renal cancer is still nephrectomy.
nephrectomy is still only observation.

Enrollment in randomized clinical trials after radical resection of RCC should be encouraged and offered to all patients eligible; an appropriate selection of patients who would benefit from adjuvant therapies remains a crucial dilemma, in particular identifying prognostic factors which might better predict the risk of relapse.

The hope of improving survival after nephrectomy has been renewed with the emerging role of targeted therapies which are currently at the forefront of new studies in an adjuvant setting for RCC. Although the international guidelines do not actually recommend any adjuvant treatment after radical RCC surgery, there is still no last word on this, pending the results of the promising ongoing clinical trials with the angiogenesis and mTOR inhibitors. The significant changes that these new drugs have made on advanced disease outcome could represent the key to innovation in terms of preventing recurrence, delaying relapse and prolonging survival after radical surgery for RCC.

References


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73. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon...