Neoadjuvant and adjuvant strategies in renal cell carcinoma: more questions than answers

Krisztian Homicsko and Dominik R. Berthold

The current standard treatment for early stage (I-III) renal cell cancer (RCC) is surgery. While the prognosis of stage I tumors is excellent, stage II and particularly stage III have a high risk of relapse. The adjuvant treatment of patients with RCC remains an area of investigation, with patient selection being a key aspect. There are currently two prognostic nomograms to establish the risk of relapse in patients with resected RCC. The results of earlier studies of adjuvant therapy, including the use chemotherapy and/or immunotherapy after nephrectomy have failed to show any benefit in the outcome of patients at risk of developing local recurrence or distant metastases. Two recent phase III trials with vaccines (autologous tumor cell vaccine and autologous tumor-derived heat shock protein peptide complex-96) have shown promising, albeit still preliminary, results. In the metastatic RCC setting, recent advances in the molecular understanding of oncogenic pathways have led to the development of new therapeutic strategies with the use of targeted therapies in the adjuvant setting. Neoadjuvant treatment is another treatment modality currently being evaluated for patients with early disease and in patients with metastatic RCC with inoperable primary tumors. The questions that remain unanswered include activity of these agents in early stages of the disease, patient selection, optimal start time of the adjuvant treatment, and finally, the optimal length of treatment. *Anti-Cancer Drugs* 22 (suppl 1):S4–S8 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Centre Pluridisciplinaire d'Oncologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Correspondence to Dominik R. Berthold, MD, Centre Pluridisciplinaire d'Oncologie-Centre Hospitalier Universitaire Vaudois, Rue de Bugnon 46, 1011 Lausanne, Switzerland
Tel: +41 21 31 48 083; fax: +41 21 31 40 200;
e-mail: Dominik.Berthold@chuv.ch

Introduction

The widespread availability and increasing use of non-invasive abdominal imaging in medicine has led to a progressive increase in the diagnoses of early asymptomatic renal cell cancer (RCC) [1]. In a recent analysis of the National Cancer Data Base (USA), the distribution of stages at diagnoses in RCC showed the following: stage I 50.6%, stages II and III 26.7%, and stage IV 22.7%, respectively [2].

The current standard treatment for early stage (I–III) RCC is surgery. Either an open or laparoscopic nephrectomy or, preferable if feasible, nephron-sparing surgery with optional regional lymph node dissection is the procedure of choice [3,4]. While the prognosis of stage I tumors is excellent, stage II and particularly stage III RCCs have a high risk of relapse. After surgical excision, 20–30% of all patients with localized tumors experience relapse [5]. The lung is the most common site of distant recurrence, occurring in 50–60% of patients. The median time to relapse after surgery is 1–2 years, with most relapses occurring within 3 years after initial diagnoses. Longer disease-free intervals between diagnosis and the recognition of metastatic disease are associated with longer projected survival.

The adjuvant treatment of patients with RCC remains an area of investigation. One key aspect for a potential adjuvant treatment in cancer patients is the selection of the population at risk. Patients with a high risk of recurrence can benefit from adjuvant treatments whereas individuals with a lower risk need to be spared from unnecessary treatments. Thus, prognostic classifications are needed. There are two prognostic, retrospectively validated nomograms, to establish the risk of relapse in patients with resected RCC: the Mayo Clinic stage, size, grade, and necrosis nomogram and the UCLA integrated scoring system (UISS). The Mayo Clinic stage, size, grade, and necrosis nomogram was devised based on a retrospective analysis of 1801 patients. In this classification, tumor stage according to the 1997 tumor node metastasis stage (TNM) system, tumor size, grade of differentiation, and presence of histological necrosis are prognostic for cancer-specific mortality [6]. The UISS stratification is based on the 1997 TNM, Fuhrman grade, and Eastern Cooperative Oncology Group performance status and allows the classification of patients into low-risk, intermediate-risk, and high-risk groups for developing recurrence or metastases after treatment of localized or locally advanced RCC [7,8]. The Mayo Clinic nomogram seems to be slightly superior to UISS in prognostic value and has shown an accuracy of 0.830 compared with 0.760 of UISS in one validation study of 388 patients [9]. The UISS is currently recommended by the National Comprehensive Cancer Network (NCCN) to assist in targeting patients

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with higher risk of recurrence for intensive surveillance with periodic imaging studies (*http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf*).

Results of earlier studies of adjuvant therapy

Earlier attempts to use chemotherapy and/or immunotherapy after nephrectomy have failed to show any benefit in progression-free survival or overall survival (OS) in patients at risk of developing local recurrence or distant metastases. Adjuvant interferon-α2b and high-dose or low-dose interleukin-2 regimens have not resulted in improvement of overall or relapse-free survival in patients with resected RCC [10–12].

As RCC is considered as one of the most immune responsive cancers in humans, several clinical protocols have tested whether the administration of vaccines prevents the progression of RCC [13]. To date, two randomized, adjuvant, clinical phase III studies have been published.

The first study tested an autologous tumor cell vaccine (Reniale) showing an improvement in 5-year progression-free survival from 67.8% in patients treated with placebo to 77.4% in patients vaccinated [$P = 0.0204$; hazard ratio (HR) ratio: 1.51; 95% confidence interval (CI): 1.02–2.24]. The vaccine used was well tolerated, with a very low incidence of serious toxicities (grade 3–4 toxicities $< 1\%$) [14]. This strategy was particularly effective in patients with large T3 and high-grade tumors (HR: 2.16; 95% CI: 1.47–3.18 and HR: 2.13; 95% CI: 1.53–2.98, respectively). A recent update of the study results has shown a statistically significant improvement in OS for patients with pT3 tumors. The median survival of patients randomized to placebo was 81 months whereas it has not yet been reached for patients treated with the vaccine ($P = 0.022$) [15].

The second trial explored an autologous tumor-derived heat shock protein peptide complex-96 (Vitespen) administered after surgical resection. The overall results of this trial have not shown a difference in the recurrence-free survival in high-risk patients. However, a trend toward a small benefit in patients with stages I and II RCC was reported (HR: 0.58; 95% CI: 0.32–1.02, $P = 0.056$).

These results, however, are still preliminary and require further validation largely because of the small number of patients included in the analysis [16]. In clinical practice, observation has remained the standard of care after nephrectomy.

Advances in the treatment of metastatic disease

Recent advances in the molecular understanding of oncogenic pathways in metastatic RCC (mRCC) have led to the development of new therapeutic strategies in this setting. Just a decade ago, the only treatment options were nephrectomy and immunotherapy with interferon-α2b or interleukin-2, with low efficacy and high toxicity. Chemotherapy has shown to be ineffective in the vast majority of patients with RCC. The discovery that most RCC harbor inactivation of the von Hippel–Lindau tumor suppressor gene by either deletion or by epigenetic suppression has led to the successful development of targeted agents in RCC. Tumors with a defective von Hippel–Lindau tumor suppressor gene have impaired degradation of the transcription factor, hypoxia-inducible transcription factor 1-α (HIF-1-α). Elevated levels of HIF-1-α increase the transcription of genes involved in angiogenesis, such as the vascular endothelial growth factor (VEGF), suggesting that targeting angiogenesis could represent a viable approach to treat RCC.

This hypothesis has been tested in the clinic using both monoclonal antibodies that bind and block VEGF, such as bevacizumab, or small molecules inhibitors of the VEGF receptor tyrosine kinase, such as sorafenib, sunitinib, and pazopanib [17–21]. The results of these studies have shown improvement of different outcome parameters such as progression-free survival and OS and have led to the regulatory approval of these drugs to treat patients with mRCC. In addition, HIF-1-α levels are increased in RCC by activation of the mammalian target of rapamycin pathway. Agents targeting mammalian target of rapamycin such as temsirolimus and everolimus also exert anti-angiogenesis effects and have been also developed and approved to treat patients with mRCC [22,23]. Overall, these drugs have a relatively favorable toxicity profile, with responses both at the primary tumor and at the metastases. Table 1 summarizes the characteristics and results of the key studies.

Current large adjuvant treatment trials

On the basis of encouraging results with new targeted therapies in mRCC, four randomized phase III clinical trials are investigating the role of targeted agents in patients with high-risk surgically resected RCC (main parameters summarized in Table 2):

(1) The SORCE trial (NCT00492258) is a multicenter, randomized, double-blind study in patients with intermediate and high risk, based on the Leibovich score (score of 3–11) with resected RCC. The study will include 1656 patients to be randomized into three treatment arms: sorafenib for 1 year versus sorafenib for 3 years versus placebo. The primary endpoint is disease-free survival (DFS). The trial is expected to be completed in 2012.
(2) The S-TRAC trial (NCT00375674) is a multicenter, double-blind, randomized study comparing sunitinib with placebo in 290 patients after nephrectomy, at high risk of relapse based on UISS criteria. The primary endpoint is DFS and the study will be completed in 2011.

Table 1 Results of phase III clinical trials of targeted therapies in metastatic renal cell carcinoma

	Patients	Treatment	DFS	OS	Comments
AVOREN	First-line, clear-cell mRCC after nephrectomy	Bevacizumab (10 mg every 2 weeks) + INF-α2a (9 MIU three times a week) vs. placebo + INF-α2a	10.2 vs. 5.4 months, HR: 0.63, 95% CI: 0.52–0.75; $P=0.0001$	HR 0.79, 95% CI: 0.62–1.02; $P=0.0670$	At time of publication, median OS for bevacizumab + INF arm was not reached
SU11248	First-line, clear-cell mRCC, ECOG PS 0–1	Sunitinib (50 mg 4/6 weeks) vs. INF-α	11 vs. 5 months, $P<0.001$	26.4 vs. 21.8 months, HR: 0.821; 95% CI: 0.673–1.001; $P=0.051$	Crossing over from INF-α was permitted, 50% of patients on sunitinib had dose reduction
TARGET	Second-line after cytokine therapy, clear-cell mRCC, ECOG PS 0–1	Sorafenib (400 mg twice a day) vs. placebo, double blind	5.5 vs. 2.8 months, HR 0.44, 95% CI: 0.35–0.55; $P<0.001$	HR: 0.72, 95% CI: 0.54–0.94; $P=0.02$	More grade 3–4 CTCAEs with sorafenib
RECORD-1	Second line after sorafenib, sunitinib, or bevacizumab for clear-cell mRCC, KPS > 70%	Everolimus once daily vs. placebo and best supportive care	4.9 vs. 1.9 months, HR: 0.3, 95% CI: 0.22–0.4; $P<0.0001$	NS, HR: 0.83, 95% CI: 0.5–1.37; $P=0.23$	
ARCC	First-line, clear-cell mRCC, KPS > 60%	Temsirolimus (25 mg intravenously, weekly) vs. INF-α vs. temsirolimus + INF-α	Temsirolimus alone vs. INF-α or temsirolimus + INF-α 5.5, 3.1, 4.7 months, respectively	Temsirolimus alone vs. INF-α or temsirolimus + INFα, HR: 0.73, 95% CI: 0.76–1.2; $P=0.008$	Combination therapy failed to show benefit while more discontinuation for toxicity
VEG105192	First–line (54%) or Second-line (46%), clear-cell mRCC, ECOG PS 0–1	Pazopanib (800 mg once daily) vs. placebo, double blind, randomized	Pazopanib vs. placebo 9.2 vs. 4.2 months, HR: 0.46, 95% CI: 0.34–0.62; $P<0.00001$	Not yet achieved	Low toxicity in a mixed patient study population

CI, confidence interval; CTCAEs, common toxicity criteria adverse events; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; INF, interferon; KPS, Karnofsky performance score; mRCC, metastatic renal cell carcinoma; NS, not significant; OS, overall survival.

Table 2 Main parameters of on-going adjuvant trials

	Population studied	Treatment	Number of patients	Primary endpoint	Predicted completion date
ASSURE	pTlb-pT4N0 pT any N+	Arm A: oral sunitinib, arm B: oral sorafenib, arm C placebo	1939	DFS	April 2016
SORCE	Leibovich score 3–11 (intermediate and high risk)	Arm I: 3 years of placebo, arm II: 1 year sorafenib and 2 years placebo, arm III: 3 years of sorafenib	1656	DFS	August 2012
S-TRAC	UISS high risk	Arm A: 1 year sunitinib, arm B: 1 year placebo	500	DFS	December 2010
SWOG-S0931	High risk and very high risk	Arm I: everolimus, arm II: placebo	1218	DFS	August 2013

DFS, disease-free survival; UISS, UCLA integrated scoring system.

(3) The ASSURE trial (NCT00326898) compares sorafenib, sunitinib, or placebo in a multicenter, double-blind, randomized study including 1332 patients. Patients with pT1b-T4 tumors or with fully resected node-positive disease will be stratified into high and very high-risk groups. The primary endpoint of the study is DFS and secondary endpoints are OS and translational studies with an estimated completion in 2016.

(4) Finally, the SWOG-S0931 trial (NCT01120249) will study 1-year everolimus versus placebo in high and very high-risk patients after radical or partial nephrectomy. This is a multicenter, randomized, double-blind study using daily everolimus with the primary endpoint of DFS and secondary endpoints of OS, toxicity, and translational studies. Monoclonal antibodies targeting tumor-associated antigens have also been considered in the adjuvant treatment of early RCC: cG250 (WX-G250), an immunoglobulin G1 antibody, targeting carbonic anhydrase IX is currently being evaluated in a phase III trial (ARISER, NCT00087022), compared with placebo after nephrectomy and results are expected in 2013 [24].

Neoadjuvant treatment

Neoadjuvant treatment is another treatment modality currently being evaluated in RCC. There are two potential clinical scenarios to investigate neoadjuvant treatment in patients with RCC (i) early RCC in which neoadjuvant treatment may lead to less extensive and potentially nephron-sparing surgery; (ii) metastatic RCC in which debulking nephrectomy of the primary tumor has been shown to increase OS. Therefore, neoadjuvant treatment in mRCC could be considered in patients with inoperable primary tumors to allow optimal debulking.

In contrast to other tumor types in which neoadjuvant treatments are part of management approaches, thus far, there is limited evidence available for neoadjuvant

Table 3 Summary of selected neo-adjuvant trials

	Patients	Treatment	Results
Sorafenib [25]	Seventeen early RCC and 13 mRCC patients before curative or CN	Sorafenib 400 mg twice a day for 1 cycle (median duration, 33 days)	Decrease in primary tumour size (median, 9.6%); 2 PR, 26 SD by RECIST; no surgical complications
Sunitinib [26]	Nineteen mRCC patients unsuitable for CN	Sunitinib 50 mg 4/6 weeks	PR in three (16%), SD in seven (37%), and PD IN 10 (53%) patients, four patients could undergo CN
Bevacizumab [27]	Fifty mRCC patients, 82% intermediate and 18% poor risk by MSKCC before CN	Two arms, phase II, bevacizumab 10 mg/kg or bevacizumab 10 mg/kg plus erlotinib 150 mg/days	Median PFS 11 months, median OS 25.4 months, 24 patients (84%) had nephrectomy
Sorafenib or sunitinib or bevacizumab [28]	MD Anderson Cancer Center, recurrent or mRCC patients before CN, 44 patients presurgical treatment, 58 CN first	Bevacizumab 10 mg/kg or sorafenib 400 mg twice a day or sunitinib 50 mg 4/6 weeks ITT, at discretion of oncologist	No increased perioperative mortality, median PFS 27.7 vs. 31.0 months in presurgical treatment vs. upfront CN

CN, cytoreductive nephrectomy; ITT, intention to treat; mRRC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

treatment in early RCC (Table 3). A recent phase II study that included 17 patients with localized RCC (stage $\geq$ III) and 13 patients with mRCC addressed the feasibility and efficacy of neoadjuvant sorafenib in nephrectomy candidates [25]. The median number of days of sorafenib administration was 33 days (1 cycle). The median decrease in the primary tumor size was 9.6%. According to Response Evaluation Criteria in Solid Tumours (RECIST), of the 28 patients evaluable for response, two patients had a partial response and 26 had stable disease, with no patients progressing on therapy and importantly, there were no surgical complications.

In patients with mRCC, there are several retrospective studies using sorafenib, sunitinib, or bevacizumab before resection of the primary tumor [26–28]. In these studies, the tested agents were safe without an increase in the surgical morbidity or perioperative complications. The studies have reported some evidence of clinical activity, although prospective phase II–III studies are warranted to confirm the efficacy. There are two phase III studies actively recruiting patients (i) The CARMENA (NCT00930033) trial that investigates the role of nephrectomy in patients with mRCC treated with tyrosine kinase inhibitors and (ii) the EORTC-30073 (NCT01099423) trial, in which patients with mRCC are randomized to either nephrectomy followed by sunitinib or sunitinib followed by nephrectomy.

Open questions that still remain

Although there are multiple randomized trials addressing the role of adjuvant and neoadjuvant treatment with angiogenesis inhibitors in patients with mRCC, a number of other significant questions remain unanswered. Thus far, antiangiogenic therapy (bevacizumab) combined with standard adjuvant chemotherapy has shown no benefit in patients with resected breast and colon cancer despite activity in advanced disease. Although the single agent activity with tyrosine kinase inhibitors in patients with mRCC is impressive and clearly superior to any other cancer type, the role of angiogenesis in early RCC is not well known and therefore it is difficult to gauge, whether these agents will be similarly effective in patients with earlier stages of the disease. Another important issue is patient selection. Thus far, the studies in the adjuvant setting are focused on patients with high-risk disease based mainly on stage and other clinical factors. There is no biomarker to predict the effectiveness of angiogenesis inhibitors in patients with RCC. If such markers exist, it would be very helpful to identify and select patients with earlier stages of the disease more likely to benefit from adjuvant treatments [29,30]. There are several markers being developed to tailor antiangiogenic therapy, although none of them has been validated prospectively in large trials. Another issue is the optimal start time of an adjuvant treatment. Moreover, it remains unanswered, whether monotherapy is sufficient or should combination treatments, such as VEGF/HIF pathway inhibitors with mammalian target of rapamycin inhibitors or tyrosine kinase inhibitors with chemotherapy, be used to achieve maximal eradication of micrometastatic disease. Finally, the optimal length of treatment is also unknown. Three phase III studies propose 1 or 3 years of treatment based on tumor relapse frequencies but not on biological follow-up with relevant markers.

Conclusion

The enthusiasm generated by the recent availability of several targeted drugs with significant activity in the setting of mRCC has led to new expectations in the adjuvant setting. Thus far, no level 1 evidence supports the use of targeted therapies in the adjuvant or neoadjuvant treatment of localized RCC. The four large randomized adjuvant clinical trials that are ongoing will address the feasibility and efficacy in localized RCC. Their results are eagerly awaited. Two randomized studies do reassess the value of nephrectomy for patients with metastatic disease in the area of effective treatments and will allow gaining insight into the value of neoadjuvant treatment. Current and future clinical trials will further define the patients at risk, the length of

treatment, the optimal combination, and finally, the appropriate follow-up and late toxicities of new targeted agents.

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