Current Treatment Options for Disseminated Renal Cell Carcinoma

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Abstract

Renal cell carcinoma (RCC) is a common urologic tumor and accounts for about 3% of all human malignancies; its incidence has increased steadily in recent decades. Because 40–50% of all RCC patients present with or will develop metastasis, the annual mortality-to-incidence ratio with RCC is significantly higher compared with other urologic malignancies. Only recently, the discovery of specific genetic alterations as well as distinct dysfunctional signal transduction pathways in the different renal cell carcinoma subtypes has enabled the development of innovative targeted drugs. Particularly those agents targeting the vascular endothelial growth factor and mammalian target of rapamycin pathways have revolutionized the treatment of advanced renal cancer. The median tumor-specific overall survival could be at least doubled in only a few years. This review discusses current data on clinical trials evaluating these innovative drugs with a focus on their efficacy in the first-line setting as well as their sequential and combined application.

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1. Introduction

Renal cell carcinoma (RCC) is a common urologic tumor and accounts for about 3% of all human malignancies, and its incidence has increased steadily in recent decades. Because the annual mortality-to-incidence ratio with RCC is significantly higher compared with other urologic malignancies [1], it is the 10th leading cause of death from cancer in the Western world. Despite improved imaging facilities and an increasingly early detection rate, up to a third of the patients still present with metastatic disease at first diagnosis [2,3]. Of the remaining two-thirds who are subjected to surgery with curative intention, about 20–30% develop systemic progression at a later date [4]. Patients with untreated metastatic renal cell carcinoma (mRCC) have a median overall survival of <12 mo, with a 5-yr survival rate <10%. Former systemic therapies were mostly cytokine based with or without cytotoxic agents. Their efficacy was limited and their toxicity considerable [5,6].

The development of therapeutic agents blocking pathways typically involved in RCC progression, such as the vascular endothelial growth factor (VEGF) pathway (eg, sunitinib, sorafenib, pazopanib, and bevacizumab) or the mammalian target of rapamycin (mTOR) pathway (temsirolimus, everolimus) has established molecular targeted therapy as the preferred therapeutic approach for most patients with advanced RCC (Fig. 1).

For first-line therapy, temsirolimus (poor prognosis patients with three of six risk factors) [7], sunitinib [8], pazopanib [9], and bevacizumab in combination with interferon (IFN)α [10,11] have been proven to be effective and are authorized in most European countries. Sorafenib has been approved for the treatment of patients after the failure of initial cytokines or for patients unsuitable for cytokine-based therapy [12]. Everolimus is currently the
standard treatment for patients after failure of at least one tyrosine kinase inhibitor (TKI) [13,14]. Whenever possible, patients should be enrolled in clinical trials.

2. Data source

A Medline search was performed to identify publications related to treatment options for disseminated RCC, using the following keywords: renal cell cancer, metastasis, surgery, targeted therapy, and adjuvant treatment. The references of the articles obtained were reviewed for potentially relevant publications.

3. Therapeutic agents

3.1. Vascular endothelial growth factor pathway

3.1.1. Sunitinib

Sunitinib was approved as a first-line therapy after a large phase 3 study had demonstrated its effectiveness in comparison with IFN monotherapy [15,16]. In this large trial with 750 patients, the median progression-free survival demonstrated a highly significant benefit for patients treated with sunitinib (progression-free survival: 11 vs 5 mo). In addition, in this trial the objective response rate for patients who received sunitinib was 47% as opposed to 12% for IFN-α patients only. Figlin et al. [16] presented updated data in 2008 that demonstrated a trend for prolonged median overall survival (26.4 vs 21.8 mo; hazard ratio [HR]: 0.82; 95% confidence interval [CI], 0.67–1.00; p = 0.051) for patients randomized to receive sunitinib compared with IFN. In the light of these data, sunitinib became the standard first-line therapy for mRCC, at least in the good and intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk evaluation prognosis patient collective.

The MSKCC criteria, which had been elaborated during the cytokine era to stratify the risk and prognosis of patients with mRCC, were reevaluated by Patil et al. [17] in 2009 for patients on targeted therapy. Including 350 patients who received sunitinib, all classic prognostic factors (hemoglobin, calcium, and lactate dehydrogenase level, general condition, and time to metastasis) could be confirmed (Table 1).

3.1.2. Sorafenib

Sorafenib is the most extensively evaluated agent in cytokine-pretreated patients. In a phase 3 trial [18], 903 patients with refractory, systemically progressive RCC who had failed a previous systemic therapy were randomized into two groups: one treated with sorafenib and the other with placebo. A significant elongation in progression-free survival of 5.5 versus 2.8 mo favoring sorafenib was demonstrated. In a prospectively planned per protocol analysis excluding patients who had received sorafenib after progressing on placebo, sorafenib significantly improved survival (17.8 vs 14.3 mo; HR: 0.78; 95% CI, 0.62–0.97; p = 0.0287). However, the role of sorafenib in untreated...
patients is still being discussed. In a randomized phase 2 study, sorafenib was compared with IFN-α in good- and intermediate-risk patients [19]. There was no significant increase in progression-free survival with sorafenib (5.7 vs 5.6 mo; HR: 1.14; 95% CI, 0.61–1.27). However, during the study, patients treated with sorafenib (400 mg/d twice daily) were allowed to dose-escalate (600 mg/d twice daily); this dose escalation prolonged progression-free survival for another 4 mo.

3.1.3. Pazopanib
Even though data from a head-to-head study comparing pazopanib with the current standard sunitinib are still pending (COMPARZ trial), pazopanib was recently approved for the treatment of mRCC in Europe. This decision was based on the results of a phase 3 trial published by Sternberg et al. [9], in which first- and second-line patients who were treated with pazopanib experienced significant higher response rates (30% vs 3%) and a longer progression-free survival compared with a placebo control group (9.2 vs 4.2 mo).

3.1.4. Bevacizumab
Bevacizumab was successfully tested in combination with IFN-α and approved as a first-line therapy in Europe. In a controlled phase 3 study (AVOREN), 649 patients were randomized to receive IFN-α plus bevacizumab or IFN-α plus placebo [10]. A significant doubling in progression-free survival for patients with IFN-α plus bevacizumab was demonstrated (10.2 vs 5.4 mo; p = 0.0001). However, patients with a poor prognosis according to MSKCC risk evaluation or mixed history did not demonstrate a significant difference in progression-free survival between the study groups.

A follow-up analysis presented at the 2009 American Society of Clinical Oncology meeting confirmed that the final progression-free survival was 10.4 versus 5.5 mo, with a response rate of 31% versus 13% favoring the combination with bevacizumab [20]. The analysis of overall survival demonstrated a median long-term survival of 23.3 mo for patients treated with bevacizumab and 21.3 mo for patients treated with IFN-α plus placebo. This difference in data was not statistically significant (HR: 0.86; p = 0.1291).

The similarly designed Cancer and Leukemia Group B (CALGB) study reported overall survival data of 18.3 mo for treatment with bevacizumab plus IFN-α versus 17.4 mo for treatment with IFN-α alone [11], which was not a statistically significant difference either. Therefore, it is certainly reasonable to consider very carefully which patients might benefit from this combined therapy. Even though analogous data are lacking, patients with solitary lung metastases and pure clear cell RCC who demonstrated a good response to cytokine-based therapy in the past might characterize a subgroup of patients that may benefit from treatment with IFN-α in combination with bevacizumab.

3.2. Mammalian target of rapamycin

3.2.1. Temsirolimus
A first-line phase 3 trial (ARCC) randomized 626 poor prognosis patients with metastatic or recurrent RCC to temsirolimus, the combination of temsirolimus plus IFN-α or IFN-α monotherapy [21]. A statistically significant prolongation of the median overall survival in high-risk patients of 10.9 versus 7.3 mo was found for temsirolimus in comparison with treatment with IFN-α as a single agent. Therefore, currently temsirolimus is a standard first-line agent for poor prognosis stage 4 RCC. Furthermore, a phase 2 trial demonstrated that patients with good or intermediate prognosis and previous IFN or interleukin therapy for advanced disease can also benefit from treatment with temsirolimus (response rate: 7%; time to progression: 5.8 mo; median overall survival: 15 mo) [22].

3.2.2. Everolimus
Recently, everolimus (RAD001), an orally administered mTOR inhibitor, gained market authorization for second-line therapy in patients who had failed treatment with one or more TKIs. Everolimus was studied after failure of TKI therapy in a double-blind placebo-controlled phase 3 trial in a total of 416 patients (RECORD-1 study; randomized 2:1 everolimus to placebo). Approximately three-quarters of these patients were at least third-line patients who had progressed on sunitinib, sorafenib, or both. Prior therapy with cytokines or bevacizumab was also allowed. The median progression-free survival with everolimus improved significantly from 1.9 to 4.9 mo (HR: 0.30; 95% CI, 0.22–0.40). No significant difference was demonstrated in overall survival (14.8 vs 14.4 mo; HR: 0.87; p = 0.16);
however, most of the placebo-treated patients subsequently received open-label everolimus [14]. In the currently conducted RECORD-2 study, everolimus is being investigated in combination with bevacizumab compared with bevacizumab plus IFN-α as a first-line therapy in patients with mRCC. The RECORD-3 evaluation of everolimus followed by sunitinib treatment will be tested against a sunitinib/everolimus sequence.

3.3. Sequence therapy

In recent years, no clinically relevant cross-resistance was found regarding sorafenib and sunitinib. Thus these agents can be effectively administered in sequence [23–30]. The optimal order remains to be determined and is currently being evaluated in the SWITCH trial. mTOR inhibitors seem to be active not only in untreated high-risk patients (demonstrated for temsirolimus [21]) but also in cytokine/TKI pretreated and refractory patients, which has particularly been shown for everolimus [14]. Bevacizumab plus IFN-α can be administered as first-line therapy for pure clear cell RCC patients only [10,31]. The best therapeutic sequence for individual patients still remains unclear; potential treatment options are shown in Figure 2. Especially considering the upcoming development and approval of several additional therapeutics in the near future (eg, axitinib, tivozanib, dovitinib), it is quite unrealistic to believe that the best treatment (sequence) for each individual patient can ever be determined, at least as long as specific biomarkers are lacking.

4. The role of surgery in metastatic renal cell carcinoma

During the cytokine era, the resection of the primary tumor prior to an IFN treatment was indisputable because it was associated with an improved efficacy of the systemic treatment as well as prolonged overall survival [32]. Moreover, the resection of metastases, whenever possible, was also the standard of care, especially if the metastases were found in only one organ site and could be removed completely (R0) [33–36]. Today, with the availability of the novel more effective targeted drugs, the role of primary tumor resection in metastatic disease as well as the resection of metastases is less clear. However, recent data indicate that neither bevacizumab [37] nor sunitinib [38–40] or sorafenib [41] affect the primary renal tumor as effectively as its metastases, which would still militate in favor of an initial tumor nephrectomy. This question is currently addressed in the randomized CARMENA and the European Organization for Research and Treatment of Cancer 30073 trials. However, Barbastefano et al. [42] found in their patient collective that the tumor nephrectomy prior to targeted treatment was particularly associated with an improved overall survival in those cases, in which the operation could remove >90% of the total tumor burden. Taken together, whenever the patient is suitable for surgical treatment and particularly a complete resection of metastatic lesions seems possible, surgery should still be considered one of the most valuable cornerstones in the treatment of mRCC.

5. Adjuvant therapy in renal cell carcinoma

IFN, interleukin-2, chemotherapeutics, tumor vaccines, and hormones have been tested in the adjuvant setting without great success. However, the role of small molecular therapeutics in an adjuvant setting of locally advanced RCC remains unclear. To date, there is no effective adjuvant agent for high-risk patients to counteract recurrence after initial surgery.

A few ongoing studies try to evaluate the principles and benefits of targeted agents in the adjuvant setting. The Eastern Cooperative Oncology Group 2805 ASSURE (adjuvant sorafenib or sunitinib in unfavorable RCC) is a double-blind trial randomizing 1923 patients to receive sunitinib, sorafenib, or placebo for 1 yr. The primary end point is disease-free survival. Patients can be included if they underwent nephrectomy with the following findings: pT1b, G3–4; pT2–4; all node-positive disease.

The S-TRAC trial compares the efficacy and safety of sunitinib versus placebo for the treatment of patients at high risk of recurrent RCC. Adjuvant sunitinib is given at
50 mg daily on a 4-wk on, 2 wk-off schedule versus placebo for 1 yr. The primary end point of the study is disease-free survival, and secondary end points are relapse-free survival, overall survival, patient-reported outcomes, and safety. A very similar trial, the PROTECT study, was started only recently to evaluate the efficacy and safety of pazopanib in the same indication.

The SORCE trial, a double-blind controlled phase 3 study, compares sorafenib with placebo in patients who underwent nephrectomy and are at high or intermediate risk of tumor recurrence. The study randomizes patients to placebo for 3 yr or sorafenib for 1 or 3 yr in a 2:3:3 ratio. The primary end point is metastasis-free survival.

First results of the ARISER study [43], which started several years ago and was designed to evaluate the efficacy of a monoclonal antibody directed against CA-IX in the adjuvant setting, are still pending.

6. Neoadjuvant and presurgical systemic therapy in advanced renal cell carcinoma

A variety of retrospective and three small prospective studies have provided important insights into the use of antiangiogenic therapy prior to nephrectomy. All of these reports confirm that the primary tumor can be responsive to systemic therapy, at least to a certain grade. A reduction of tumor size can lead to complete onologic resection through downstaging/downsizing of the tumor. In a subgroup of patients with locally advanced disease, Thomas et al. [44] reported a tumor size reduction between 0% and 24%, with a mean decrease of 9.5%. Other studies showed similar results with a downsizing efficacy of 13–14% for different targeted agents [45,46].

In patients with inferior vena cava thrombosis caused by a tumor thrombus, Karakiewicz et al. [47] described a significant reduction of the thrombus extension in the inferior vena cava after sunitinib therapy, enabling an easier surgical procedure. Few data are available on the downsizing to avoid radical nephrectomy [48].

Although surgical tumor resection after targeted therapy is feasible with low morbidity in most cases, significant complications can occur as a potential consequence of compromised tissue or vascular damage [44]. Margulis et al. [49] reported a complication rate of up to 39% for cytoreductive nephrectomy following targeted therapy.

Further studies are needed to address unresolved issues, such as which agent provides the best tumor reduction for which patient and/or minimizes the perioperative risk, the optimal time of systemic treatment (“downsizing”) prior to surgery, and whether neoadjuvant therapy can improve the curative potential of tumor nephrectomy in patients with locally advanced renal cancer.

7. Conclusions

The discovery of specific genetic alterations as well as distinct dysfunctional signal transduction pathways in the different RCC subtypes has enabled the development of several innovative targeted drugs. Particularly those targeting the VEGF and mTOR pathways have revolutionized the treatment of advanced renal cancer; the median tumor-specific overall survival could be at least doubled in only a few years. However, the treatment with these novel drugs is still palliative and expensive. Most combinations are unacceptably toxic, and we still lack indicators to predict which patient profits most from which agent in which sequence and dose rate. These remaining questions must be addressed in future research.

Conflict of interest

The authors have nothing to disclose.

References


alpha (IFN-a) as first-line treatment of metastatic renal cell carcino-


