Future developments in renal cell carcinoma

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Background: The development of targeted agents has substantially improved prognoses for patients with metastatic renal cell carcinoma (mRCC). Four targeted agents are approved for the treatment of mRCC in Europe (bevacizumab given in combination with interferon-alfa, sorafenib, sunitinib and temsirolimus) and a number of investigational agents have shown potential in this setting.

Design: This report will review completed and ongoing clinical trials in mRCC designed to investigate the efficacy of targeted agents in sequential and combination therapies and in the adjuvant and neoadjuvant settings.

Results: A phase III trial, in which 71% of patients received prior sunitinib treatment, has indicated that everolimus can be used after sunitinib, the reference standard of care for first-line therapy, to extend progression-free survival. Phase I/II studies have provided preliminary data on the efficacy of sequential and combination therapies with targeted agents in mRCC. Several phase III studies investigating targeted agents in sequential and combination therapies and in the adjuvant and neoadjuvant settings are planned or ongoing, and data are awaited with interest.

Conclusions: Data suggest that sequential and combination therapies with targeted agents have potential in patients with mRCC. Ongoing research will help to optimise the use of targeted therapies in this setting.

Key words: clinical trials, metastatic renal cell carcinoma, sunitinib malate, targeted agents, tyrosine kinase inhibitor

introduction

In Europe, more than 63 000 new cases of renal cell carcinoma (RCC) and 26 000 deaths were reported in 2006 [1]. Historically, the prognosis for patients with metastatic RCC (mRCC) has been poor, with a 5-year survival rate of ~10% [2]. Until recently, cytokine therapy with interleukin-2 or interferon-alfa (IFN-α) was the only effective treatment available for mRCC; however, cytokine therapy conferred median overall survival (OS) of just 13.3 months [3] and was associated with substantial toxicities [4].

The development of targeted agents has changed the management of mRCC substantially. These agents include the oral, multitargeted receptor tyrosine kinase inhibitor (TKI) sunitinib malate (SUTENT®; Pfizer Inc.), which is approved multinational for the first- and second-line treatment of mRCC [5]. In a phase III trial in 750 patients with previously untreated mRCC, sunitinib 50 mg/day was administered according to the standard 6-week cycle of 4 weeks on treatment followed by 2 weeks off treatment (Schedule 4/2) and was associated with median OS of >2 years [6, 7]. As discussed in more detail in the article by Cora Sternberg [8], sunitinib is now the established reference standard of care for the first-line treatment of mRCC, and is recommended in international treatment guidelines in this setting [4, 9]. In addition to sunitinib, three other targeted agents are also available in Europe for the treatment of mRCC: sorafenib tosylate (Nexavar®; Bayer Healthcare), temsirolimus (Torisel®; Wyeth Pharmaceuticals) and combination therapy with bevacizumab (Avastin®; F. Hoffmann-La Roche) plus IFN-α.

The introduction of targeted agents into clinical practice has led to dramatic improvements in prognoses for patients with mRCC. Furthermore, evidence from clinical trials and clinical experience is assisting the tailored use of these agents, according to patients’ individual profiles. Ongoing research in mRCC is ensuring that this process of optimising the use of targeted agents is evolving. Numerous studies are in progress to further define the role of targeted agents in mRCC when used in sequence or in combination, as well as examining additional settings, such as their use as adjuvant therapy.

This article will review how the management of mRCC can be further improved. The potential use of targeted agents, in sequence or in combination, will be discussed as well as the integration of novel targeted agents, such as everolimus and axitinib, into the treatment algorithm [10, 11]. The potential role of targeted agents in the adjuvant and neoadjuvant settings will also be examined and the expected impact of these developments on the management of RCC in the future will be discussed.

how to improve the management of mRCC

sequencing targeted agents

Utilising targeted agents in sequence has several potential benefits. First, sequential use enables a treatment continuum to
be achieved, with the goal of maintaining patients on treatment without progression for as long as possible. Secondly, sequential therapy should enable full dosages of targeted agents to be administered, ensuring that patients are exposed to optimal drug levels without adverse effects on tolerability. Thirdly, RCC is well characterised in terms of the numerous pathways involved in its pathogenesis. As such, targeting different pathways through sequential therapy should offer benefits in terms of overcoming resistance to individual agents.

Several clinical studies have investigated the use of targeted agents in sequence in patients with mRCC (prospective studies are listed in Table 1). Findings to date indicate an absence of cross-resistance between the different targeted agents [10–13, 15, 16], suggesting the clinical potential of this strategy in mRCC.

The first randomised phase III study to investigate sequential targeted therapy in mRCC compared everolimus [an oral inhibitor of mammalian target of rapamycin (mTOR)] with placebo, in conjunction with best supportive care, in patients who had progressed on sunitinib, sorafenib or both agents [11]. Of note, 71% of the study population had received prior therapy with sunitinib. Among patients receiving everolimus, median progression-free survival (PFS) was 4.9 months, compared with 1.9 months with placebo treatment [hazard ratio (HR) 0.33; 95% CI 0.25–0.43; \( P < 0.001 \); Figure 1] [17]. Improvements in PFS with everolimus relative to placebo were observed across all Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk groups. Among patients who had received prior therapy with sunitinib, median PFS with everolimus was 3.88 months, compared with 1.84 months with placebo (HR 0.34; 95% CI 0.23–0.51; \( P < 0.001 \)). In the group of patients who had previously received sorafenib (55% of the study population), a median PFS of 5.88 months was observed with everolimus, compared with 2.83 months with placebo (HR 0.25; 95% CI 0.16–0.42; \( P < 0.001 \)) [16].

The TKI sorafenib is recommended as second-line therapy for mRCC, following the failure of cytokine treatment [4–7, 9], on the basis of phase III trial data [18]. Several reports are now available examining the use of sorafenib as second-line therapy after treatment with another targeted agent, and these data suggest additional activity with sorafenib in this setting. Two retrospective analyses investigated the sequential use of sunitinib and sorafenib (or sorafenib and then sunitinib), and both analyses suggested a lack of cross-resistance between these agents, supporting their use in sequence [15, 16]. A further study examined the second-line use of sorafenib in 37 patients with mRCC who had received first-line treatment with sunitinib or bevacizumab [12]. No objective responses were observed; however, 15 of 29 evaluable patients (52%) exhibited some tumour shrinkage and median PFS was 3.8 months.

Data from an exploratory phase II study in 61 patients have suggested a lack of cross-resistance between sunitinib and bevacizumab [13]. Analysis of vascular endothelial growth factor (VEGF) levels suggested that sunitinib may inhibit signalling pathways involved in bevacizumab resistance [13].

Table 1. Prospective trials of sequential targeted agents in metastatic renal cell carcinoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study type</th>
<th>Population</th>
<th>N</th>
<th>ORR, %</th>
<th>CBR, %</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus versus placebo</td>
<td>Ph III</td>
<td>Sunitinib and/or sorafenib-refractory</td>
<td>410</td>
<td>1</td>
<td>64</td>
<td>4.9 months (versus 1.9 months for placebo)</td>
<td>Not reached (versus 13.01 months for placebo)</td>
</tr>
<tr>
<td>Sorafenib [12]</td>
<td>Ph II</td>
<td>Sunitinib- or bevacizumab-refractory</td>
<td>37</td>
<td>0</td>
<td>NR</td>
<td>3.8 months</td>
<td>NR</td>
</tr>
<tr>
<td>Sunitinib [13]</td>
<td>Ph II</td>
<td>Bevacizumab-refractory</td>
<td>61</td>
<td>23</td>
<td>75</td>
<td>30.4 weeks</td>
<td>47.1 weeks</td>
</tr>
<tr>
<td>Axitinib [10]</td>
<td>Ph II</td>
<td>Patient refractory to: sunitinib and sorafenib (Su/So), cytokines and sorafenib (Cy/So), sorafenib alone (So)</td>
<td>62</td>
<td>Su/So: 7.1; Cy/So: 27.6; So: 25.0</td>
<td>Su/So: 7.1 months; Cy/So: 9.1 months; So: 7.8 months</td>
<td>Su/So: 11.5 months; Cy/So: 18.5 months; So: 9.2 months</td>
<td></td>
</tr>
<tr>
<td>Ongoing/planned trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Axitinib versus sorafenib [14]</td>
<td>Ph III</td>
<td>After failure of first-line therapy</td>
<td>540</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus versus sorafenib [14]</td>
<td>Ph III</td>
<td>Sunitinib-refractory</td>
<td>440</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

CBR, clinical benefit rate; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; NR, not reported; Ph, phase.
Sequential treatment has also been investigated with the VEGF inhibitor, axitinib, in a phase II study involving 62 patients with mRCC who had progressed on other agents (sunitinib and sorafenib, cytokines and sorafenib or sorafenib alone) [10]. Median PFS was 7.1 months, 9.0 months and 7.7 months, respectively, in patients who had received prior treatment with sunitinib and sorafenib (n = 14), cytokines and sorafenib (n = 29), or sorafenib alone (n = 16; Figure 2). A phase III trial is planned to investigate axitinib in the second-line setting [14]. The AXIS trial will compare axitinib [5 mg twice daily (b.i.d.)] with sorafenib (400 mg b.i.d.) in ~540 patients with mRCC who have experienced failure on a first-line treatment (including sunitinib, bevacizumab + IFN-α, temsirolimus or cytokines). A study comparing sorafenib (400 mg b.i.d.) with temsirolimus (25 mg i.v. once weekly) will also investigate sequential therapy in an estimated 440 patients who have experienced treatment failure on first-line sunitinib [14].

Clinical evidence to date suggests that sequential targeted therapy is possible in patients with mRCC, conferring improved responses without cross-resistance. Data from the phase III trial with everolimus, in which 71% of patients had received prior sunitinib, indicate that the sequence of sunitinib followed by everolimus has clinical potential. This sequence may gain increasing use with the widespread adoption of sunitinib as first-line therapy in mRCC.

**Figure 2.** Kaplan–Meier estimates of (A) median progression-free survival and (B) median overall survival with axitinib in patients with metastatic renal cell carcinoma according to prior therapy [reproduced with permission from 10].

### Combination therapy with targeted agents

Combination therapy with two or more targeted agents may offer advantages with respect to maximising clinical benefit. In particular, combining agents that target several pathways simultaneously may lead to improved clinical outcomes. However, the clinical benefit must be balanced against a potential increase in toxicity associated with combining targeted agents.

Sunitinib has been investigated in patients with mRCC in combination with gemicitabine in a phase I study [19]. The combination was well tolerated, at the maximum tolerated combined dose of sunitinib 50 mg/day and gemcitabine 1250 mg/m² administered on a 2 weeks on, 1 week off schedule, and demonstrated promising antitumour activity. Sunitinib is also undergoing evaluation in combination with the oral protein kinase C-β inhibitor, enzastaurin, in a phase II study in patients with previously untreated mRCC [14]. Furthermore, a dose-finding study is investigating the efficacy and safety of sunitinib combined with the anti-cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA4) monoclonal antibody, CP-675,206, in patients with mRCC [14].

Several small-scale studies have investigated the combination of bevacizumab with other targeted agents. Two phase I studies have demonstrated antitumour activity with bevacizumab plus sorafenib. At the first evaluation in a study in 48 patients with mRCC, the median time to progression was 11.2 months and the partial response (PR) rate was 46% [20]. In 39 patients with advanced solid tumours, PR or disease stabilisation for ≥4 months was observed in 59% of assessable patients, and a PR was achieved in one of three patients with RCC [21]. However, this combination required dose reduction of both agents, with bevacizumab appearing to increase sorafenib-related toxicities, including hand–foot syndrome and hypertension [20, 21]. This suggests crossover toxicity due to potential interruption of vascular signalling pathways, such as VEGF, by bevacizumab and sorafenib. Everolimus, in combination with bevacizumab, has been investigated in a phase II study in patients with mRCC who had received prior treatment with sorafenib and/or sunitinib. The combination demonstrated efficacy and tolerability in this second-line setting [22]. In contrast, preliminary results from studies combining bevacizumab with sunitinib in patients with mRCC have reported some concerning toxicities that required dose reductions [23, 24].

Two randomised phase III trials are ongoing or planned to further investigate combinations of targeted agents. The first of these is comparing the combination of bevacizumab plus temsirolimus with the standard therapy of bevacizumab plus IFN-α as first-line therapy in ~800 patients with mRCC [14]. In the second study (transformed to a phase II study with an expected enrolment of 360 patients), patients with previously untreated mRCC will be randomised to bevacizumab plus IFN-α or bevacizumab plus everolimus [14]. A further phase II trial, TORAVA, is assessing sunitinib monotherapy versus bevacizumab plus temsirolimus versus bevacizumab plus IFN-α as first-line therapy for mRCC [14].

To date, phase I/II studies have provided preliminary indications of the efficacy of targeted agents in combination; however, additional larger studies are needed to fully assess the
efficacy and safety of these regimens. It is also important to consider potential follow-up options following the use of targeted agents in combination. Should resistance develop to a combination therapy, it may be challenging to find an appropriate follow-up treatment for affected patients.

**potential role of targeted agents in the adjuvant and neoadjuvant settings**

**adjuvant therapy**

Recurrence rates in patients with localised RCC range from 35% to 65% [25]. Based on their efficacy in the metastatic setting, it has been proposed that adjuvant therapy with targeted agents may delay disease progression and improve survival. This is the focus of three ongoing clinical trials in patients with RCC (Table 2) [14].

The Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC) trial will assess the effectiveness of 1 year of adjuvant treatment with sunitinib versus placebo in patients with high-risk RCC, as defined by the UCLA Integrated Staging System (Figure 3). The Sorafenib with Placebo in Patients with Resected Primary Renal Cell Carcinoma (SORCE) trial is a three-arm study that will compare 3 years of treatment with sorafenib against 1 year of treatment with sorafenib plus 2 years of placebo against placebo for 3 years in patients with resected primary RCC with no residual disease but a high or intermediate risk of relapse (Leibovich score 3–8). The Adjuvant Sorafenib Sunitinib Unfavorable Renal Cell Carcinoma (ASSURE) trial will assess the effect of adjuvant sunitinib, sorafenib or placebo in patients with non-metastatic RCC. This trial will also examine whether any beneficial effects are extended to patients with non-clear-cell carcinomas. Additionally, data may assist in the identification of biological markers to help predict the likelihood of relapse and improve the selection of patients who are likely to benefit from adjuvant therapy. The results of these studies are eagerly awaited to help define the potential role of targeted agents in the adjuvant setting across patient groups with different risk profiles.

**neoadjuvant therapy and the use of targeted agents with nephrectomy**

The efficacy of targeted agents in the metastatic setting suggests that these agents may have potential for tumour downstaging in the neoadjuvant setting. Indeed, preliminary reports have indicated the efficacy of sunitinib in this setting [26, 27].

Two phase III studies investigating the integrated use of sunitinib and nephrectomy in patients with mRCC are planned (Figure 4) [28]. The first of these studies, which is planning to enroll 576 patients with mRCC, will aim to answer the question

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**Table 2. Ongoing studies with targeted agents in renal cell carcinoma in the adjuvant setting [14]**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Start date</th>
<th>Projected completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE: adjuvant sorafenib or sunitinib for unfavorable renal cell carcinoma</td>
<td>1132</td>
<td>May 2006</td>
<td>April 2010</td>
</tr>
<tr>
<td>SORCE: sorafenib versus placebo in patients with resected primary RCC at high/intermediate risk</td>
<td>1656</td>
<td>June 2007</td>
<td>August 2012</td>
</tr>
</tbody>
</table>

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**Figure 3.** Study design of the Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC) trial [14]. UISS, University of California Los Angeles Integrated Staging System; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status.

**Figure 4.** Planned phase III studies integrating nephrectomy and sunitinib for the management of metastatic renal cell carcinoma. (A) CARMENA trial; (B) EORTC trial [27]. EORTC, European Organisation for Research and Treatment of Cancer; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival.
of whether sunitinib alone is non-inferior to nephrectomy followed by sunitinib with respect to OS. In the second study, 440 patients with mRCC will be randomised to nephrectomy followed by sunitinib or sunitinib followed by nephrectomy, with PFS as the primary endpoint. Results from these studies will help to better define the role of nephrectomy in patients with mRCC receiving treatment with targeted agents.

**conclusions**

The prognosis for patients with mRCC has improved significantly with the introduction of targeted agents, such as sunitinib. However, there is an opportunity to further optimise treatment by investigating new indications for currently available agents and by developing novel therapies.

Clinical trials are currently in progress to investigate the most appropriate agents for sequential treatment and combination therapy, and to determine whether these approaches can be used to further improve clinical outcomes. In terms of sequential treatment, robust phase III clinical trial results now show that another targeted agent, everolimus, can be used after prior TKIs such as sunitinib (the majority of patients who receive targeted therapy receive first-line treatment with this agent) to further extend PFS.

Research is also focusing on whether there is a role for targeted agents in the adjuvant and neoadjuvant settings. Increasing the indications for targeted agents as well as the development of new agents may allow many more patients to gain optimal clinical benefit from targeted agents in the future.

**disclosures**

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**references**