Integrated therapy of kidney cancer

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Historically, treatment options for metastatic renal cell carcinoma (RCC) have been limited because of inherent tumor resistance to chemotherapy and radiotherapy. The only approved drug for RCC in the past 30 years has been high-dose interleukin-2. Its benefit is observed in a small percentage (20%–25%) of highly selected good performance status RCC patients. The treatment of advanced RCC has recently undergone a major change with the development of potent angiogenesis inhibitors and targeted agents. In fact, advanced RCC is a highly vascular tumor associated with expression of vascular endothelial growth factor (VEGF); thereafter, antiangiogenic strategies have become an attractive approach. Several multitargeted tyrosine kinase inhibitors (sorafenib and sunitinib) have already been approved for the treatment of advanced RCC; bevacizumab, a monoclonal antibody anti-VEGF, has shown promising clinical activity. Temsirolimus, a derivative of rapamycin (CCI-779), has also shown a survival advantage over interferon in advanced, poor-prognosis RCC patients. The aim of this review is to describe these agents in terms of mechanisms of action, efficacy, and toxicity profile and also to analyze future development strategies.

Key words: metastatic renal cell carcinoma, kidney cancer, chemotherapy

introduction
Renal cell carcinoma (RCC) comprises a histologically diverse group of solid tumors, together making up ~3% of all adult neoplasms [1]. Clear cell (CC) RCC is the most common histologic subtype, comprising up to 80% of RCC specimens [2]. Approximately 60% of CC RCC tumors have an inactivated von-Hippel–Lindau (VHL) tumor suppressor gene, through either somatic mutation (~50% of RCC tumors) or promoter methylation (~10% of tumors). In addition, silencing of a remaining normal allele by hypermethylation or other epigenetic mechanisms may explain some of the remaining cases of sporadic CC RCC [3–6].

The treatment of election for localized RCC is surgical resection. Since 1969, the standard of care has been open radical nephrectomy. However, continuous advancement in surgical techniques, imaging technology, and pathological understanding of disease progression has caused radical changes in the treatment of localized RCC [7, 8].

- Adjuvant therapy for localized disease

There is currently no role for adjuvant therapy after surgical resection. Adjuvant radiation, both external beam and intraoperative, has been examined and added no significant benefit on outcome [9, 10]. Neo-adjuvant radiation has likewise shown no benefit [11]. Adjuvant immunotherapy and chemoimmunotherapy for localized disease also have shown no benefit. In patients at high risk for recurrence following nephrectomy, novel techniques for improving outcomes have been examined. Among these techniques, promising results come from tumor ‘vaccines’ through the elicitation of a specific immune response against their derivative cancer. Phase III trials are currently ongoing [8].

Two trials are investigating new agents in the adjuvant setting: the ASSURE trial in which patients with nephrectomy specimens showing high grade T1b/T2 or any grade T3/T4 are randomized to receive sorafenib, sunitinib, or placebo for 1 year. The planned accrual of 1300 patients began in 2006 [12]. The SORCE trial compares sorafenib with placebo in patients with resected primary RCC at high or intermediate risk of relapse. Patients are stratified by risk factors and then randomized into three groups: sorafenib for 3 years, placebo for 3 years, and sorafenib for 1 year followed by placebo for 2 years. When available, results from these studies will help define the role of adjuvant therapy in RCC [12].

- Treatment of metastatic disease

Chemotherapy is poorly active in RCC. The reason for the relative resistance of RCC to chemotherapy is likely related to the high level of expression of the drug transporter P-glycoprotein [13] and of other drug transporters, such as the multidrug resistance-associated proteins [14, 15].

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Many agents have been tested with most showing response rates of <10% [16, 17]. One regimen showing some activity is 5-fluorouracil (5-FU) and gemcitabine. One phase II study reported a 17% response rate and median progression-free survival (PFS) of 28.7 weeks in heavily pretreated patients [18]. A larger multi-institutional phase II study of capcitabine and gemcitabine showed a response rate closer to rates of 10% [19]. Few single agents from those reported in a comprehensive review by Yagoda et al. [20] appeared to have activity above the background: 5-FU [overall response rate (ORR) of 10% for infusional 5-FU alone and 19% for 5-FU in combination with interferon (IFN)], the related compound floxuridine (response rates ranging from 0% to 43%, with an average rate of 12%), and vinblastine (seven trials with infusional vinblastine yielded an ORR of 7%, and no responses in three trials).

Hormonal agents have also been used in systemic therapy, with disappointing results (ORR 2%) [8].

Up until 2005, the only approved drug for RCC in the past 30 years has been high-dose interleukin-2 (HDIL-2), a cytokine that activates T cells and natural killer cells. Its benefit is observed in a small percentage (20%–25%) of highly selected good performance status RCC patients [21]. On the basis of the phase II studies [22, 23], the Food and Drug Administration (FDA) approved HDIL-2 therapy for advanced RCC treatment. Unfortunately, HDIL-2 treatment is associated with significant toxicity: capillary leakage is almost universal and leads to a broad spectrum of serious side-effects, such as hypotension, through vascular permeability and nitric oxide production. However, studies comparing HDIL-2 to low-dose interleukin-2 (LDIL-2) treatment schedules (including intravenous and subcutaneous) demonstrate reduced toxicity. However, LDIL-2 therapy does not result in durable complete responses (CRs), thus defeating one important goal of immunotherapy [24].

IFN is an alternative immunomodulatory agent with multiple potential mechanisms of antitumor activity: activation of cytotoxic T cells and natural killer cells, induction of major histocompatibility complex class I antigens, inhibition of cell proliferation and angiogenesis, and modulation of gene expression.

Two trials compared IFNα with vinblastine and megestrol, respectively, confirming its activity in RCC. Survival benefit was 7.5 months when compared with vinblastine [25] and 2.5 months when compared with megestrol [26]. The evidence-based data regarding use of IFNα in treating RCC have recently been reviewed [27]. Response rates are probably between 5% and 15%, with a general better tolerability than HDIL-2. Unfortunately, the duration of response is usually limited to 4–6 months [28].

A study by Negrier et al. compared IFNα with intravenous IL-2 and their combination. The 425 randomized patients demonstrated a significant increase in event-free survival for the combination. However, no significant difference in overall survival (OS) was reported [29]. As expected, intravenous IL-2 therapy, alone or in combination, was associated with significant toxic effects. For this reason, most subsequent studies of novel therapies use IFNα for comparison.

Thus, treatment options for metastatic RCC remain limited because of inherent tumor resistance to chemotherapy and radiotherapy and only a limited subset of patients treated with immunotherapeutic agents benefit from these cytokines with modest objective response rates.

For this reason, in recent years new therapeutic strategies have been investigated in metastatic RCC.

**RCC biology and rationale for target therapy**

Both sporadic and inherited forms of CC RCC are associated with mutations in the VHL tumor suppressor gene, located on chromosome 3p [3]. Individuals who inherit one defective copy of the VHL gene have a substantial risk for developing RCC and a variety of other tumors [4]. Up to 75% of these patients have biallelic loss of function and mutation of VHL genes, and up to 20% exhibit expression inactivation by hypermethylation [5, 6].

The VHL gene product plays a key role in the ubiquitination of hypoxia-inducible factor 1α (HIF-1α) [6], which regulates the expression of several genes in response to hypoxic stress [3]. Under normal conditions (i.e. with wild-type VHL and normal oxygen tension), HIF-1α is enzymatically hydroxylated. HIF-1α is subsequently ubiquitinated by the VHL protein complex and degraded within proteasomes. Under hypoxic conditions, HIF-1α is not hydroxylated and cannot bind and be ubiquitinated by the VHL protein complex. Biallelic inactivation of VHL (as occurs in CC RCC) likewise prevents degradation of HIF-1α.

In addition, HIF-1α activity is regulated by growth factor and cell adhesion pathways, including the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway and the Ras/Raf/mitogen-activated protein kinase pathways [3–6].

Once stabilized, HIF-1α translocates into the nucleus, where it links to the constitutively present HIF-1β to form the active transcriptional factor HIF-1 heterodimer. HIF-1 binds to a variety of additional transcriptional cofactors that activate transcription of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), platelet-derived growth factor (PDGF), glucose transporters (e.g. GLUT-1), transforming growth factor α (TGF-α) (ligand for EGFR), and erythropoietin [30]. Many of these proteins are involved in angiogenesis, survival, pH regulation, and glucose metabolism. The absence of functional VHL protein in the inherited and sporadic forms simulates hypoxia with resultant constitutive upregulation of these genes (Figure 1).

**molecular-targeted agents: clinical results**

A number of targeted agents have been evaluated, including monoclonal antibodies (mAbs) and tyrosine kinase inhibitors, such as sunitinib and sorafenib. The mTOR inhibitor
Temsirolimus demonstrated also activity against mRCC. The results of phase III randomized studies with these agents are summarized in Table 1.

Trials of single agents targeting EGFR, including gefitinib, cetuximab, and others, failed to show activity [40–42]. One randomized trial found no improvement in survival for lapatinib, an inhibitor of EGFR/Erb2 tyrosine kinases, over hormonal therapy [43]. A subset analysis carried out in patients with tumors showing overexpression of EGFR indicated benefit in this group, [43] and may be considered as hypothesis generating. Limited experience of imatinib, which inhibits PDGFR without VEGFR inhibition, failed to show single-agent activity [44].

**sorafenib**

Sorafenib is an inhibitor of the RAF-1 protein and VEGFR and PDGFR. In a ‘randomized discontinuation’ trial, 202 mRCC patients were treated with 12 weeks of sorafenib 400 mg b.i.d., and those patients with tumor burden change no more than 25% of baseline [stable disease (SD)] were randomized to placebo or to continuation of sorafenib. A PFS advantage of 24 versus 6 weeks (P = 0.0087) was shown in the randomized cohort of 65 patients at 12 weeks after randomization [35]. The most commonly reported grade 3/4 toxic effects were hand–foot syndrome, fatigue, and hypertension. The incidence of grade 3/4 toxic effects seemed to be lower in the phase III trial when compared with the phase II study [34, 35] but this may be because patients with several adverse risk factors were excluded from the phase III trial.

In another randomized phase III trial comparing sorafenib with placebo, ~900 patients with treatment-refractory metastatic clear-cell RCC (mRCC) were accrued [45]. The interim analysis, conducted after 353 events, demonstrated that the median PFS duration was 24 weeks in the sorafenib arm compared with 12 weeks in the placebo group (P < 0.000001). Independent review of the response data demonstrated that 80% of patients were progression free in the sorafenib arm [2% partial response (PR) and 78% SD] compared with 55% in the placebo arm [0% PR and 55% SD]. The most common adverse effects included hand–foot skin reaction (26%), diarrhea (30%), alopecia (23%), fatigue (18%), nausea (14%), and hypertension (8%) [45]. An update of the impact of sorafenib on OS was reported [46]. As of the data cutoff, there were 367 deaths. The median OS was 19.3 months for sorafenib and 15.9 months for placebo. Although these data did not attain a level of significance at this interim analysis, a favorable trend in survival benefit has been observed. After the interim analysis, patients treated with placebo crossed over to sorafenib. This likely has an effect on the survival analysis [46].

**Figure 1.** VHL regulation in renal cell carcinoma. VHL, von Hippel–Lindau; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin.

**Table 1.** Phase II/III data from key trials of bevacizumab, sorafenib, sunitinib, and temsirolimus in metastatic renal cell carcinoma (modified by Rini [31])

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study population</th>
<th>No. of patients</th>
<th>PFS</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab versus placebo</td>
<td>Second line</td>
<td>116</td>
<td>4.8 versus 2.5 months</td>
<td>ORR (%) 10 versus 0%</td>
</tr>
<tr>
<td>Bevacizumab + erlotinib</td>
<td>First line</td>
<td>104</td>
<td>8.5 versus 9.9 months</td>
<td>ORR (%) 13 versus 14%</td>
</tr>
<tr>
<td>Sorafenib versus placebo</td>
<td>Second line</td>
<td>905</td>
<td>5.5 versus 2.8 months</td>
<td>ORR (%) 2 versus 0%</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Second line or later</td>
<td>202</td>
<td>24 weeks</td>
<td>ORR (%) 4%</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Second line</td>
<td>63</td>
<td>8.7 months</td>
<td>ORR (%) 40%</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Second line</td>
<td>106</td>
<td>8.1 months</td>
<td>ORR (%) 44%</td>
</tr>
<tr>
<td>Sunitinib versus IFNA</td>
<td>First line, all MSKCC (1), risk group</td>
<td>750</td>
<td>11 versus 5 months</td>
<td>ORR (%) 31 versus 6</td>
</tr>
<tr>
<td>Temsirolimus (T) versus T/ IFN</td>
<td>First line, modified MSKCC (1), poor-risk group only</td>
<td>626</td>
<td>3.7 (T ± IFN) versus 1.9 months (IFN alone)</td>
<td>10.9 versus 8.4 versus 7.3 months (P = 0.0069, T versus IFN)</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; ORR, overall response rate; IFN, interferon. (1) Memorial Sloan-Kettering Cancer Center, New York, NY.

*Partial response 25% of the sum of products of the maximum perpendicular diameters of measured lesions lasting for a minimum of 1 month with no progression of any lesion or appearance of new lesions.

*RICIST criteria.

*Third-party independent review.

*Investigator assessed.

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**Table 1.** Phase II/III data from key trials of bevacizumab, sorafenib, sunitinib, and temsirolimus in metastatic renal cell carcinoma (modified by Rini [31])
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On the basis of these data, sorafenib was approved by the FDA as monotherapy for advanced RCC in December 2005. A randomized phase II trial of sorafenib versus IFN-α in untreated metastatic RCC is ongoing to define the activity of sorafenib in this setting [47]. Additional investigations are underway to better define the efficacy of sorafenib as first-line therapy, adjuvant therapy or in combination with other targeted agents or cytokines.

sunitinib

Sunitinib (SU11248) is an oral multitargeted inhibitor of VEGFR and PDGFR. Sunitinib showed an ORR of ~40% in patients with cytokine-refractory metastatic RCC in two sequential phase II trials with a combined median PFS of 8.2 months [36, 37]. In the first trial of 63 patients, 25 (40%) achieved PRs with sunitinib, and an additional 17 (27%) had SD lasting at least 3 months. Median time to progression (TTP) was 8.7 months [95% confidence interval (CI) 5.5–10.7], and median OS was 16.4 months [36].

In a second, larger single-arm trial, 105 assessable patients received a median 7 months of therapy; the investigator-assessed response rate was 44%. A further 23 patients (22%) had SD for at least 3 months. The median duration of response for the 46 responders was 10 months, and median investigator-assessed PFS was 8.1 months (95% CI 5.5–10.4). An independent third-party assessment resulted in 36 patients with PR (34%; 95% CI 25–44) and a median PFS of 8.3 months (95% CI 7.8–14.5 months) [37].

Serious gastrointestinal complications, including gastrointestinal perforation, rarely occurred in patients with intra-abdominal malignancies treated with sunitinib. Vascular toxic effects, such as hypertension and bleeding, are biologically plausible on the basis of the known effects of VEGF on blood pressure and existing vasculature.

A phase III randomized trial of first-line sunitinib versus IFN-α in 750 patients with metastatic clear cell RCC found statistically significant improvements in ORR and PFS with sunitinib compared with IFN-α. Median PFS as assessed by an independent review was 11 months in the sunitinib arm versus 5 months in the IFN-α arm. The response rate was 31% for sunitinib versus 6% for IFN-α (P < 0.0001). The response rate by investigator assessment was 37% for sunitinib versus 9% for IFN-α (P < 0.000001) [38]. The results demonstrated a significant improvement in PFS and objective response rate for sunitinib over IFN in first-line treatment of mRCC. The toxicity profile was similar to that reported in second-line studies. On the basis of these data, sunitinib is proposed as the standard therapy for first-line treatment.

Sunitinib was approved by the FDA in January 2006. Data from the phase III trials of sorafenib and sunitinib are not at present mature enough to allow definitive evaluation on OS.

A different dosing schedule of sunitinib is being studied. In a study of 88 patients treated with a continuous daily sunitinib 37.5 mg dose, preliminary efficacy data showed some degree of tumor shrinkage in the majority of patients [48]. Sunitinib administered at this continuous dose of 37.5 mg was well tolerated, with only a few patients requiring treatment breaks or dose reduction [48]. However, further investigation is required before the continuous dosing regimen is recommended.

temsirolimus

mTOR, a large polypeptide kinase, is an another therapeutic target. mTOR is a downstream component in the PI3K/Akt pathway, which acts by regulating translation, protein degradation, and protein signaling. VEGF-mediated endothelial cell proliferation requires the activity of PI3K, indicating a direct antiangiogenic pathway [49]. mTOR has also been identified as an upstream activator of HIF, preventing degradation and increasing HIF activity [50]. Preclinical data with a derivative of rapamycin (temsirolimus) have shown antitumor effects in renal and other tumor types [51].

In a randomized phase II trial, 111 patients with advanced, heavily pretreated, refractory mRCC were treated at three different dose levels (25.0, 75.0, and 250 mg) of temsirolimus (CCI-779) [52]. Seven percent of patients achieved a PR or CR. No significant differences in outcome were related to the dosage. The median TtP was 5.8 months with a median OS for the entire population of 15.0 months [22]. Temsirolimus was combined with IFN-α in a phase I/II clinical trial of 71 mRCC patients. PRs were observed in 11% of all patients with a median TtP of 9.1 months [53].

A phase III randomized trial compared temsirolimus as a single agent (25.0 mg) versus temsirolimus (15.0 mg) plus IFN-α versus IFN-α as first-line treatment in patients with poor-risk features [39]. Poor-risk eligibility for the trial was on the basis of modified MSKCC criteria [54]. Six hundred twenty-six patients were randomly assigned. The median OS for temsirolimus was 10.9 months compared with 7.3 months with IFN and 8.4 months with temsirolimus plus IFN. There was a significant improvement in survival for temsirolimus compared with IFN (P = 0.0069, hazard ratio = 0.73) [39]. Further studies are needed to define the role of temsirolimus in first-line therapy for patients with a more favorable prognosis combined with other targeted agents or as sequential therapy after treatment with sunitinib or sorafenib.

bevacizumab

Bevacizumab (BV) is a humanized mAb agent that binds and neutralizes all the major isoforms of VEGF-A. In a randomized, double-blind phase II trial, two dose levels of the antibody were studied (3 and 10 mg/kg) versus placebo, and therapy was administered every 2 weeks. Eligible patients included those who had a histologic confirmation of CC carcinoma and either had received previous therapy with IL-2 or for whom the use of IL-2 was contraindicated. A total of 116 patients were randomly assigned to the three treatment groups. At the time of a planned interim analysis, the median TtP was significantly increased to 4.8 months in the patients receiving the 10-mg/kg dose of BV compared with 2.5 months for placebo. Responses were noted only in the group treated with BV at 10 mg/kg, with four patients (10%) having partial tumor regressions [32].

Two large randomized trials currently underway are comparing PFS and OS in untreated patients receiving the combination of BV plus IFN-α or IFN-α alone (with or without placebo). These two randomized phase III trials have completed accrual and are powered to demonstrate an increase of median OS. The activity of BV monotherapy will not be addressed.
directly, however, except for the suggestion of improved PFS seen in first-line therapy in a randomized phase II trial [33].

The value of BV monotherapy in untreated RCC was also tested in a randomized phase II trial of BV ± erlotinib. The ORR was 13% and median PFS with BV monotherapy was 8.5 months [33]. No improved clinical outcome was observed by the addition of erlotinib to BV.

Initial studies with BV showed that it was generally well tolerated with the most common toxic effects being hypertension and asymptomatic proteinuria. Hypertension was managed with standard antihypertensive agents [55]. Other less common toxic effects were noted in large studies in colorectal cancer and included arterial thromboembolic events (myocardial infarction 1.5%, cerebrovascular accident 0.5%) and gastrointestinal perforations (2.0%) [56].

other promising agents

There are several VEGFR-targeted tyrosine kinase inhibitors under study. Pazopanib completed phase I evaluation and is currently evaluated in a randomized discontinuation trial in the United States and in a pivotal phase III trial in Europe. Another is AG013736 that showed a 40% response rate in a phase II trial conducted in 52 patients with cytokine-refractory mRCC [57]. Yet another phase II trial is ongoing with AG013736 in patients with progressive disease after sorafenib.

RAD001 (everolimus) is an orally active mTOR inhibitor that showed antitumor activity in achieving objective response as well as prolonged TTP in single-arm phase II study in heavily pretreated patients [58]. A randomized trial comparing RAD001 with placebo in patients who progressed to sunitinib or sorafenib therapy is planned.

VEGF-trap, a fusion protein composed of VEGFR fused to human immunoglobulin G (IgG), binds serum VEGF. A phase I trial of VEGF-trap in 15 patients with advanced solid malignancies did not produce objective responses, but one patient with RCC had SD for >6 months [59]. Further assessment of activity for this agent in a phase II trial for patients with mRCC is underway.

Infliximab is a chimeric human/mouse antibody targeting tumor necrosis factor α. Early phase II trial results reported some efficacy in patients unresponsive to immunotherapy. Out of the 15 assessable patients, three had PRs and another two had SD at a median follow-up of 7 months. No significant toxicity was observed [60].

rationale for combined multitargeted therapy

RCC is an angiogenesis-dependent disease, so antiangiogenic strategies have become an attractive approach. Sunitinib, sorafenib, BV, and temsirolimus downregulate proangiogenic factors and induce high objective response rates (sunitinib), significant increases in PFS (sunitinib, sorafenib and BV), or improved OS (temsirolimus). It has been recently hypothesized by Folkman [61] that the tumor growth arrest by the use of a broad-spectrum single, multitargeted agent is capable simultaneously to block several angiogenesis pathways or, alternatively, by combinations of different selective drugs.

However, since sunitinib and sorafenib are themselves antiangiogenic multitargeted agents and clinical trials have shown that the majority of patients will develop acquired resistance it should be investigated whether the best strategy is up-front combined treatments or sequential therapy.

combined therapy: rationale and approaches

Two different concepts for combined targeted therapy for RCC have been indicated. The so-called ‘horizontal blockade’ aimed to concurrently target numerous molecules of the HIF axis in attempt to prevent cancer cell proliferation, to promote apoptosis, and to inhibit tumor-induced angiogenesis. Thus, the targets may be represented by a number of the involved mediators (EGFR, VEGFR2, PDGFRβ) at the different cell-type levels (tumor cell, endothelial cell, pericyte). A similar rationale exists for targeting TGF-β signaling pathways because TGF-β is also overexpressed when VHL is disabled. However, in clinical trials the use of inhibitors of the receptor for TGF-β, the EGFR, failed to demonstrate efficacy. The other strategy is the ‘vertical blockade’ because the same pathway (HIF and VEGF, VEGF and VEGFR) is targeted at two or more different levels by more agents in attempt to overcome the developing of compensatory feedback loops. However, these feedback mechanisms likely represent only one of the causes of RCC resistance to antiangiogenic agents. Other ways to suppress the HIF axis include the arrest of its translation by means of mTOR inhibitors (temsirolimus, everolimus) or by accelerating its breakdown with heat shock protein antagonists (ansamycins) [62] in combination with agents targeting the products of the HIF downstream (BV, sunitinib, sorafenib). Phase I and II trials evaluating the safety and efficacy of these combinations are underway. However, affecting the tumor vascular supply, antiangiogenesis agents induce pathophysiologic changes in variables such as blood flow, pH, and oxygenation that could have influences on the activity of combining multiagents [63].

multitargeted anti-VEGF/anti-EGFR

TGF-β, a ligand for EGFR, is frequently overexpressed in RCC and has been shown to be a growth factor for RCC cells independently of stroma [64]. Preclinical studies demonstrated important interactions between EGFR and VEGF signaling pathways. They act both directly and indirectly on tumor cells, and combining drugs targeting both the targets confer additional clinical benefit. EGFR has been detected in the endothelial cells of tumor vasculature in preclinical studies [65]. VEGF is also downregulated by EGFR inhibition [66, 67] and a recent study indicates that blockade of VEGF may also inhibit the EGFR autocrine signaling [68]. Therefore, EGFR could be an additional target for therapeutic intervention. The combined use of agents such as erlotinib (EGFR-tyrosine kinase inhibitor) and BV (VEGF inhibitor) that target different signaling pathways and affect different cell types (tumor cell and endothelial cell) may result more effective and delay the overcoming of resistance.

In a multicenter phase II trial, 63 patients with metastatic CC RCC were treated with BV 10 mg/kg intravenously every 2 weeks and erlotinib 150 mg orally daily. Clinical benefit was obtained in 25% (1 CR and 14 PRs) and 61% (SD) of the
patients. The median and 1-year PFS were 11 months and 43%, respectively. After a median follow-up of 15 months, median OS has not been reached with 60% of patients alive at 18 months control. The combination seemed to be more active than each agent alone and generally well tolerated. Only two patients discontinued treatment because of toxicity (skin rash), while grade 1/2 skin rash and diarrhea were the most frequent treatment-related toxic effects [33]. However, when the same combination was tested in a randomized phase II trial including 104 patients with untreated disease, the objective response rates were 13% and 14% and PFS was 8.5 and 9.9 months for patients treated with BV plus erlotinib and those treated with BV alone, respectively [33]. The hypothesis of combining an EGFR-blocking agent with a VEGF-VEGFR-blocking agent although failed to be effective remains appealing. That is because many other anti-EGFR agents can be employed (gefitinib instead of erlotinib or antibodies targeting the receptor) in combination with either sorafenib or sunitinib and results may be different due to their different spectrum and mechanisms of action on different targets.

conclusions

Approaches that may maximize the clinical benefit of new therapeutic strategies include rational patients selection, the choice of combination regimens, implementation of novel trial designs with appropriate clinical end points, and identifying surrogate predictive markers of response.

An emerging issue is the development of resistance to these agents. Resistance to or failure of antiangiogenic agents is currently defined by the evidence of progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Clinically, it is recognized that not all ‘resistances’ are identical. An anecdotal example is the use of sunitinib in 61 metastatic RCC patients resistant to prior BV-based therapy, that has showed an ORR of 23% and overall tumor shrinkage rate of 74%, supporting the clinical hypothesis that VEGF and related receptor signaling are still therapeutically relevant after VEGF ligand blockade [69]. This is also confirmed by the proven activity of sunitinib or sorafenib on failure of prior therapy with antiangiogenic agents [70]. Several trials are ongoing in patients with metastatic RCC who are refractory either to BV, sorafenib, or sunitinib. These data will provide insight into the degree of clinical cross-resistance to these therapies and perhaps begin to identify an optimal sequence of agents. Interestingly, recent preclinical studies indicate that fibroblast growth factor (FGF) upregulation is important to the development of resistance to antiangiogenic therapy. This indicates that blockade of FGF in combination with inhibitors of VEGF and PDGF may be an approach to prevent development of resistance or for treatment of resistance once it occurs. Dual FGF and VEGF inhibitors are entering early clinical trials [71].

Another important aspect for the improvement of efficacy of targeted therapies is the careful preselection of patients most likely to respond to anti-VEGF therapy. CC histology has been an inclusion criterion in nearly all trials on the basis of the biology of VHL inactivation and subsequent VEGF overexpression, which is confined to this histology [31]. Predictive surrogate biomarkers of response are also being investigated. Studies have found a correlation between circulating VEGF levels and poor prognosis in many tumor types [72, 73], but results to date in metastatic RCC are inconclusive. Plasma VEGF levels were measured in the BV trial [55] although no significant correlation was found between pretreatment levels and clinical response or TtP in either of the BV groups. Soluble VEGFR-2 levels weakly correlated with exposure to sunitinib therapy [74]. Additionally, in these trials of sunitinib, VEGF levels increased in patients with PRs compared with those experiencing SD or progression. It can be hypothesized that a greater degree of tumor regression is associated with more effective VEGFR inhibition (as reflected in lower soluble VEGFR-2 and higher VEGF protein levels), but this hypothesis requires further investigation. Regarding VHL status and response to VEGF-targeted agents, an initial report in metastatic RCC patients treated with VEGF-targeting agents did not find a correlation between VHL inactivation and response [75]. However, the subset of patients with VHL methylation or a mutation predicted to truncate or shift the VHL reading frame (and thus presumably disrupt VHL protein function) had a longer median TtP versus patients with no methylation, truncation, or shift in the VHL reading frame (13.3 versus 7.4 months, respectively; P = 0.06). Additional molecular profiling studies, including assessment of VHL activation status and RNA/protein expression studies, are ongoing to determine whether certain tumor expression profiles are predictive of response or resistance to therapy [12].

In conclusion, current cytokine-based therapies of RCC are effective for subsets of patients and may be associated with significant toxicity. It is likely that the standard of care for advanced RCC will continue to evolve. Further investigation of the molecular effects (i.e. pharmacodynamics) of these agents (e.g. on immune function) and the molecular basis for response of each single patient are the keys to improve the efficacy of antiangiogenic agents in future years [76–78].

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