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REVIEW ARTICLE

Systemic Therapy in Renal Cell Carcinoma: Advancing Paradigms

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ABSTRACT: The 21st century has seen an explosion in the development of agents for renal-cell carcinoma (RCC), a malignancy previously considered refractory to systemic therapy beyond cytokine therapy. At this time, there are six US Food and Drug Administration (FDA)-approved agents available. In addition, there was a recent favorable review by the FDA's Oncologic Drugs Advisory Committee of a next-generation vascular endothelial growth factor receptor (VEGFR) inhibitor, axitinib (Inlyta); other agents are in advanced testing. Moreover, while VEGF- and mammalian target of rapamycin (mTOR)-targeted therapies have become the mainstay of RCC treatment, other new molecular targets and therapeutic approaches are being developed. The availability of active agents also brings opportunities for additional clinical maneuvers, such as neoadjuvant and adjuvant therapy, as well as a need for decisions on combinatorial therapeutics in the advanced disease setting. Together, these developments and the issues they raise pose important challenges for oncologists and cancer biologists, given the limited number of patients and resources available for studies and the urgent clinical needs of the patients and families affected by RCC.

Introduction

Renal cell carcinoma (RCC) had historically been regarded as a disease that was refractory to therapy once surgical options had been exhausted. It is recognized that early intervention with nephrectomy results in excellent long-term survival. In 2005, the US Food and Drug Administration (FDA) approved the first small molecule therapy for kidney cancer, sorafenib(Drug information on sorafenib) (Nexavar). Five other approvals have followed. The introduction of these agents, which have inhibitory activity against the family of vascular endothelial growth factor receptors (VEGFRs) or the mammalian target of rapamycin (mTOR), has shifted treatment paradigms for advanced disease. Prior to this, only interferon (IFN)-alfa and interleukin (IL)-2 were used, both of which have always been viewed as highly toxic therapies with a small chance of long-term benefit. Despite the advances, however, none of the newer therapies have yielded a long-term solution for patients. Even today, the majority of patients present with locally advanced or metastatic disease, and the 5-year survival is on the order of 10% to 50%.[1] More than 60,000 new cases of RCC were expected to be diagnosed in 2011, with more than 13,000 deaths expected in the same year.[2]

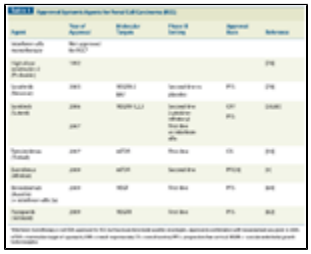
This article will review the recent advances that form the current framework of therapy for RCC, as well as summarize key areas of progress and innovation in the evolving treatment paradigms for this disease.

Current Guidelines for Management of Advanced RCC

The current guidelines from the National Comprehensive Cancer Network (NCCN) continue to identify nephrectomy as an important initial consideration even in the setting of metastatic disease.[3] The current recommendations call for removal of the kidney and/or oligometastatic sites of disease prior to initiation of systemic therapy when possible. For patients with clear-cell carcinoma, there are a number of approved agents, including sunitinib (Sutent), temsirolimus (Torisel), everolimus (Affinitor), bevacizumab(Drug information on bevacizumab) (Avastin; used with IFN-alfa), pazopanib (Votrient), high-dose IL-2 (Proleukin), and sorafenib (Nexavar). Despite the availability of these treatment options, clinical trials are an important consideration even in patients with untreated metastatic disease. All of the above agents have demonstrated some activity in the second-line setting. Most have shown activity in the first-line setting with the exception of everolimus, for which phase III clinical data are in the second-line setting (after progression on a tyrosine kinase inhibitor [TKI]).[4] The questions that remain unanswered by the current guidelines are: (1) what the rationales are for selecting one agent over another in the first- and/or second-line setting; (2) what role signal transduction inhibitors play in the perioperative setting; (3) what role nephrectomy plays in metastatic disease; and (4) what combinations or sequences of these therapies are effective in patients.

Signal Transduction Inhibitors

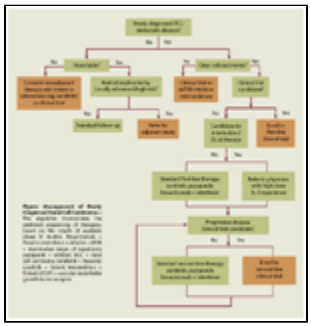
TABLE 1



Approved Systemic Agents for Renal Cell Carcinoma (RCC)

Given the hypervascularity of RCC and the knowledge of the tumor's biology we have gained from understanding Von Hippel–Lindau syndrome and its associated molecular pathways, VEGF- and mTOR-directed therapies have become a mainstay of RCC treatment (Table 1). The emergence of a number of active agents has created a new series of issues for oncologists. Before the introduction of signal transduction inhibitors (STIs), oncologists were faced with decisions about how to proceed in the face of cytokine therapy's limited benefits. Now oncologists must select which of the approved treatments should be used as first-line therapy, and which should then be used subsequently. The Figure shows a flow chart that represents current practice guidelines for management of RCC.

FIGURE



Management of Newly Diagnosed Renal Cell Carcinoma

Despite the growing number of therapies, significant gaps in our understanding of RCC treatment remain, and these gaps require investigation. Thus, enrollment in clinical trials needs to be supported by the community at large. At present, there are three treatments approved for first-line therapy: sunitinib, pazopanib, and bevacizumab with IFN-alfa. In the absence of head-to-head comparisons, it is difficult to determine with certainty which of these is best suited for a particular patient, given the current approach to RCC classifications. Some information may be gleaned from ongoing studies, but given the limited pool of patients and the number of active agents in use and in development, there is a need to bring to the population of RCC patients the most important and informative trials possible.

Additional and more potent agents are in active development—additional STIs as well as immunotherapies. These agents have the potential not only for sequential use but also combinatorial use. Table 2 summarizes phase II and phase III trials in RCC for therapies in advanced testing.

VEGFR Inhibitors: Axitinib (Inlyta), Tivozanib (AV-951, KRN-951), Cediranib (AZD2171)

TABLE 2

Agents in Advanced Development for Renal Cell Carcinoma

Following the introduction of sorafenib, a series of VEGFR- targeted STIs has followed. Given the tremendous efficacy of these compounds, continued refinements have been made to drugs active on this signaling axis. These drugs share toxicities with other VEGF-/VEGFR-targeted agents, including hypertension, asthenia, and diarrhea.

Axitinib is an indazole derivative that is a highly effective inhibitor of the family of VEGF receptors (VEGFR-1, -2, and -3), and of platelet-derived growth factor receptor (PDGFR)-beta and c-Kit.[5] It has demonstrated activity following sorafenib and cytokine therapy.[6] Given emerging trends in RCC therapy, an international phase III study (AXIS) was initiated for patients with disease refractory to sunitinib, bevacizumab with IFN-alfa, temsirolimus, or other cytokine-based therapies. In the AXIS study, 723 patients were randomly assigned to receive axitinib (n = 361) or sorafenib (n = 362). Treatment with axitinib was associated with a progression-free survival (PFS) of 6.7 months, compared with 4.7 months for sorafenib (hazard ratio [HR], 0.665; $P < .0001$).[7] These data were presented and reviewed favorably at an FDA advisory board meeting in December 2011.

Like axitinib, tivozanib is another orally available, ATP-competitive, small molecule inhibitor of VEGFR-1, -2, and -3, with inhibition in the picomolar range. In the nanomolar range, tivozanib inhibits phosphorylation of c-Kit and PDGFR-beta but has limited activity against other type III receptor tyrosine kinases (RTKs).[8] A randomized discontinuation trial of tivozanib was conducted that included clear-cell and non–clear-cell RCC.[9] Median PFS was 12.5 months for patients with clear-cell carcinoma. At the initial report of this study, median PFS had not been reached for patients with papillary RCC; median PFS for patients with other subtypes was 5.4 months. The overall response rate (ORR; complete response [CR] + partial response [PR]) and stable disease (SD) rate were 29% and 56%, respectively, for patients with clear-cell RCC; 18% and 82% for patients with papillary RCC; and 17% and 57% for patients with other non-clear subtypes. For patients with clear-cell RCC, median PFS was 14.8 months. The phase III study (TIVO-1) in which tivozanib was compared with sorafenib in patients who had not been exposed to STIs has been completed; the results are pending. As with sunitinib, hypothyroidism has been reported as an adverse event related to this drug.

Cediranib is a third pan-VEGFR inhibitor that has shown promising activity. In a preliminary report of a single-arm phase II study of cediranib in treatment-naive RCC, 12 of 32 evaluable patients (38%) had a PR, and 15 patients (47%) had SD, yielding a benefit rate of 85%.[10] In a randomized, double-blind, phase II trial in the United Kingdom (UK), 71 patients with RCC were randomized 3:1 to cediranib or placebo.[11] At 12 weeks, the investigators noted a highly significant difference in mean percentage change in tumor size between the study and control groups (-20% vs +19%, $P < .0001$). Of the 18 patients in the placebo arm, 14 crossed over to cediranib; of these 14 patients, 10 had tumor reduction. In the cediranib arm, 34% achieved a PR, and 47% had SD. Adverse events were typical for VEGFR inhibitor therapy, but 87% of patients required a dose reduction or pause at a median time of 29 days because of toxicities, including diarrhea (88%; 13% grade 3 or higher) and hypertension (61%; 19% grade 3 or higher). Given the level of availability of targeted agents in the UK at the time this study was designed and initiated, the use of a placebo arm was still considered acceptable. With a number of approved treatments now available globally, it is improbable that future randomized studies in metastatic RCC will include placebo arms, due to ethical concerns.

Non-TKI VEGF Inhibitors: Aflibercept (VEGF Trap, AVE 005), Ramucirumab (IMC112B)

Aflibercept is a soluble decoy receptor incorporating domains of both VEGFR-1 and -2 fused to the Fc region of human IgG1. Thus, aflibercept binds all isoforms of VEGF-A and placental growth factor (PlGF) with high affinity.[12] Aflibercept has completed phase I testing and has moved to phase II testing in RCC.[13,14] The randomized phase II study tests two doses of aflibercept and is expected to complete accrual by 2016.

Ramucirumab is a fully human, high-affinity monoclonal antibody to the extracellular domain of VEGFR-2.[15] Its binding prevents ligand binding. A phase II trial evaluating ramucirumab in TKI-refractory RCC completed accrual in 2011. The final report on this important study is not yet available.

Fibroblast Growth Factor Receptor Inhibitors: Dovitinib (TKI1258, CHIR-258), BIBF 1120, Lenvatinib (E7080), Regorafenib (BAY 73-4506)

The family of fibroblast growth factor receptors (FGFRs) is known to be overexpressed in RCC.[16] Activating mutations of FGFRs and their ligands have been associated with neoplastic progression and

tumor vascularization in RCC. This pathway is believed to potently inactivate angiogenesis in the stromal compartment parallel to VEGFR inhibition, while also directly antagonizing FGFR-driven proliferation in tumor cells.

Dovitinib is an orally bioavailable inhibitor of FGFR-1,-2, and -3; VEGFR-1, -2, -3; and PDGFR-beta.[17] A phase II study has been completed in patients with unresectable or metastatic RCC who have received previous VEGFR-TKI therapy. In a preliminary report, 8% of evaluable patients experienced a PR and 8% had SD for 4 months or more, yielding a benefit rate of 16% in the second-line setting. Median PFS and overall survival (OS) were 6.1 months and 16 months, respectively.[18] There is currently a phase III study of dovitinib vs sorafenib underway for patients who have been treated with both a VEGF-targeted agent and an mTOR inhibitor. This study is expected to complete accrual in May 2013.

BIBF 1120 is an inhibitor of VEGFRs, PDGFRs, and FGFRs.[19] Of 10 RCC patients in a phase I study of BIBF 1120, 1 patient had a CR, 1 had PR and the majority of the remaining 8 patients had SD.[20] An ongoing phase II study comparing BIBF 1120 with sunitinib in the first-line setting for RCC was recently completed. Results are eagerly anticipated.

Lenvatinib is another orally bioavailable inhibitor of multiple receptor tyrosine kinases, including VEGFRs, PDGFR-beta, FGFR-1, and c-Kit. [21] This agent is still in early development and has completed phase I testing in advanced solid tumors to determine dosing. In this phase I dose-escalation study of 27 patients, common adverse events were hematuria, fatigue, hypertension, increased transaminase levels, headache, proteinuria, diarrhea, and increased lactate dehydrogenase.[22] Of the 25 evaluable patients, there was 1 PR in a patient with colon cancer, and 21 patients with SD. The patient with a PR achieved this reduction at cycle 4 and continued for a total of 10 cycles, at which time progression of disease was noted. An ongoing phase I/II study with a randomized phase II portion is evaluating lenvatinib alone or in combination with everolimus in patients with RCC who are refractory to VEGF-targeted treatment. Accrual should be complete by September 2013.

Regorafenib is another orally bioavailable TKI with activity against multiple proangiogenic signals, including the FGFR, VEGFR, and PDGFR families, as well as c-Kit, RET, and B-RAF.[23] A phase II trial of regorafenib for therapy-naive RCC has been completed. In a preliminary report on 33 evaluable patients, 27% experienced a PR and 42% had SD, for a benefit rate of 69%.[24] Common treatment-related adverse events for all enrolled patients were hand-foot skin syndrome, fatigue, mucositis, hypertension, rash, alopecia, diarrhea, dysphonia, and anorexia.

Angiopoietin-TIE2 Inhibitor: AMG386 (2xCon4[C])

While VEGF and the VEGFR family of receptors are strongly associated with angiogenesis, there remain a number of additional signaling pathways that may drive this process and that are amenable to pharmacologic intervention; these include the angiopoietin-TIE2 axis.[25] Ang-1, Ang-2, and Ang-4 are the known ligands for the TIE2 receptor expressed on vascular endothelial cells. AMG386 is a neutralizing peptibody targeted against Ang-1/2 that prevents interaction with the TIE2 receptor.[26]

In a phase I study, AMG386 demonstrated antitumor efficacy, with treatment-related adverse events of fatigue and peripheral edema. Of the 29 evaluable patients, there was 1 who experienced a PR and 16 patients with SD. The PR was noted at week 68 in a patient with refractory ovarian cancer. After 156 weeks of treatment, she withdrew from the study with a continued PR. Unlike with VEGF-targeted therapies, the incidence of hypertension with AMG386 was low and not considered treatment-related.[25] A phase Ib study evaluated AMG386 combined with sunitinib or sorafenib in patients with RCC.[25] An interim analysis showed 1 CR, 7 PRs and 6 patients with SD among those

receiving AMG386/sunitinib (n = 15); and 5 PRs and 9 patients with SD among those receiving AMG386/sorafenib (n = 17). While both sunitinib and sorafenib have demonstrated clinical benefit for patients with RCC, these phase I data suggested the possibility of a more potent antitumor effect gained from the addition of AMG386 (as compared to monotherapy with the VEGFR STIs) without substantial increase in harm. Given the high level of activity and acceptable toxicity, the combination was pursued in more advanced testing.

In a phase II trial, 152 treatment-naive patients were randomized 1:1:1 to receive sorafenib combined with AMG386 (10 or 3 mg/kg) or placebo once weekly; ORR was 38%, 37% and 24%, respectively, although PFS was similar for all three arms.[27]. This response rate can be compared with the 10% PR rate observed in the phase III study of sorafenib in RCC. After making this comparison, it appears that despite the recognized activity of sorafenib, the addition of AMG386 does appear to augment its antitumor effect. Thus, a combination such as this may be worth additional study. An ongoing phase II trial is evaluating AMG386 combined with sunitinib as first-line therapy in metastatic RCC (mRCC), or for cytokine-refractory mRCC; the expected completion date is sometime in 2014.

AKT Inhibitors: MK-2206

AKT has long been viewed as a convergence point for multiple oncogenic and pro-angiogenic signals. To date, few effective inhibitors of AKT have been developed, mainly because of excessive clinical toxicity. MK-2206 is a novel targeted small molecule that is a putative allosteric inhibitor of AKT activation.[28] A randomized phase II study comparing MK-2206 vs everolimus as second-line therapy following VEGF-targeted therapy is now underway. Dose-limiting toxicities of this agent included skin rash, nausea, pruritus, hyperglycemia, and diarrhea.[28]

MET Inhibitor: Foretinib (GSK136089, GSK089, XL880)

MET overexpression has been implicated as a pro-oncogenic and tumor survival mechanism in a number of tumor models, including RCC—and especially in non–clear-cell carcinomas, including chromophobe and papillary RCCs.[29] A *MET* mutation in RCC is considered rare outside of lung carcinomas and papillary RCC.[30] Foretinib is an orally available inhibitor of MET and the VEGFR family. A trial in patients with papillary RCC has been completed, and results are currently pending. Patients in this study were stratified based on the status of MET pathway activation (activation *MET* mutation, MET [7q31] amplification, or trisomy 7). In a preliminary report of this study, of 35 evaluable patients, there were 4 who experienced confirmed PRs and 27 patients with SD.[31] In addition to MET status, the investigators will report on the utility of shed MET, VEGF, and shed VEGFR2 as pharmacodynamic markers of foretinib activity.

Immunotherapy

IFN-alfa and IL-2 have continued to be considered active and usable therapies in RCC. The historic use of these agents and the observation of long-term complete remissions following treatment in a small number of patients have kept them in the armamentarium for RCC. The toxicity of these immunotherapies has made them less desirable than VEGF- and mTOR-targeted therapies. However, RCC is still considered an immunologically active disease in which immunotherapy holds promise. Thus, a number of noncytokine strategies have been and are being explored.

IMA901

IMA901 is a therapeutic cancer vaccine that consists of synthetic RCC tumor-associated peptides and that has been shown to cause T-cell activation. In a phase I study, 30 patients with stage III or IV RCC

were each given 8 intradermal IMA901 vaccinations over 64 days. In this study, T-cell responses were measured in peripheral blood using IFN ELISPOT, human leukocyte antigen (HLA) multimer analysis, and CD4+ Foxp3+ regulatory T-cell levels. One patient had a PR and seven had SD; patients in whom multiple T-cell responses were elicited had better clinical outcomes.[32,33]

A randomized phase II study evaluated IMA901 (17 intradermal vaccinations over 9 months) with or without a single dose of cyclophosphamide(Drug information on cyclophosphamide) (300 mg/m^2) administered prior to the first vaccination in patients with cytokine- or TKI-refractory RCC.[34] After 6 months, the disease control rate was 31% in cytokine-refractory patients and 12% in TKI-refractory patients. While the impact of pretreatment cyclophosphamide was not reported at the initial presentation of the trial data, pretreatment cyclosphosphamide did appear to trend toward better overall survival. In patients who had received previous cytokine therapy, the OS rate at 18 months was 83% in those who received pretreatment cyclophosphamide vs 68% in those who did not receive this pretreatment.

IMPRINT is an ongoing phase III trial of IMA901 in combination with sunitinib for first-line treatment of RCC. Approximately 330 patients will be randomly assigned to receive IMA901 either with or without sunitinib. The primary endpoint of this study is overall survival, with secondary endpoints including PFS, safety and tolerability, and cellular immunomonitoring to assess T-cell response to IMA901.

AGS-003

AGS-003 is an autologous cell-based therapy in which mature dendritic cells are collected and electroporated with CD40L and autologous amplified tumor RNA.[35] A phase II study of AGS-003 with sunitinib in newly diagnosed RCC was completed.[36] The combination was well tolerated with no grade 3 treatment-related adverse events reported. Of 21 patients at poor or intermediate risk, 2 experienced a PR and 11 had SD; median PFS in this population was 12.5 months. This effect correlated with a decrease in the percentage of T-regulatory cells and a concurrent expansion of CD28+ effector memory cytotoxic T-lymphocytes, which may have been responsible for the overcoming of tumor-induced immunosuppression.[37] The magnitude of this immunologically mediated clinical effect parallels the PFS seen with sunitinib alone[38] and is likely to be biologically unrelated. Thus, a phase III randomized, blinded study is planned that will compare sunitinib alone vs sunitinib with AGS-003 in newly diagnosed patients.

Anti-CTLA-4 antigen: ipilimumb (Yervoy)

CTLA-4 (CD52) is an inducible receptor expressed by T cells that ligates the B7 family of molecules (primarily CD80 and CD86) on antigen-presenting cells.[39] It serves as a natural inhibitor of T-cell activation and is overexpressed on cancer cells, including RCC cells. Suppression of this immune repressor was hypothesized to decrease a cancer's ability to avoid immune surveillance.

Ipilimumab is a monoclonal antibody against CTLA-4 that has been tested in a number of cancers, including RCC. In a phase II RCC study, tumor regression was noted. However, this phenomenon was associated with major gastrointestinal and endocrine toxicities that have been attributed to iplimumab.[40]

PD-1 antibody: BMS-936558 (MDX-1106, ONO-4538)

B7 homolog 1 (B7-H1) is a factor that participates in T-cell costimulation, functioning as a negative regulator of immunity.[41,42] It is expressed by aggressive RCC, displaying prognostic importance.[43] B7-H1 impairs host immunity by interaction with the Programmed Death-1 receptor (PD-1). PD-1 is

expressed on activated T cells, and like B7-H1, it is also upregulated in high-risk RCC. It is thought that this interaction may contribute to immune dysfunction in patients with RCC.[44]

BMS-936558 is a fully human monoclonal antibody to PD-1. In a phase I dose-escalation study of 39 patients with advanced refractory solid tumors, BMS-936558 showed antitumor activity, including a PR in 1 patient with RCC.[45] In a second phase I study, 126 patients, including 18 with RCC, were treated with escalating doses of BMS-936558.[46] Of 16 patients with RCC who received a 10-mg/kg dose of BMS-936558, 5 achieved an objective response, with 1 CR; 6 had SD for > 4 months. The most common adverse events attributed to this agent include depressed CD4+ counts (36%), lymphopenia (26%), fatigue (15%), and musculoskeletal events (15%).

An ongoing, randomized, blinded phase II study is evaluating three doses of BMS-936558 in patients with RCC who have received prior antiangiogenic therapy. The estimated study completion date is April 2013.

Combinatorial Therapies

STI combinations

Issues have been raised about the sequencing of effective agents to optimize outcome. Following treatment with sunitinib, both everolimus and sorafenib have been associated with improvement in PFS in patients with metastatic RCC.[47] Even as third-line or later therapy, these drugs continue to show excellent tolerability, allowing for continuation of therapy.[48] These observations have led most investigators to recommend the sequencing of therapies unless and until there is high-level evidence to support the safety and efficacy of a combinatorial approach. Despite the growing need for guidance on the optimal sequencing of available therapies, the limited number of cases together with the growing number of treatments makes it unlikely that definitive trials will be performed comparing variations in sequencing. Thus, treating oncologists are left with guidance from the available phase III studies (summarized in Figure).

Some investigators have proposed that, in contrast to sequential administration, combinations may yield synergy and hence more potent clinical activity. Combinations of STIs have been proposed that pair agents having either horizontal relationships (eg, VEGFR + epidermal growth factor receptor [EGFR]) or vertical relationships (eg, VEGF + VEGFR). The initial attempts at combination therapy, including combinations of bevacizumab with sorafenib[49] and sunitinib,[50] resulted in unacceptable toxicity. Since that time, investigators have opted to determine whether synergy in RCC exists with other, more horizontal combinations. Phase II studies have shown promising results for bevacizumab in combination with mTOR inhibitors.[51]

mTOR inhibitors+ VEGF inhibitors

A phase I trial of tivozanib and temsirolimus in VEGF inhibitor–refractory RCC was performed. The investigators were able to achieve full doses of both agents without dose-limiting toxicities (DLTs). Clinical activity included a 28% PR rate and 64% with SD.[52] Of note, in the phase III study of temsirolimus vs interferon vs a combination of the two, the objective response rate for temsirolimus alone was 8.6%.[53]

Not all combinations have run as smoothly. In a phase I/II trial of sorafenib/everolimus, therapy required dosing at 50% of monotherapy doses because of toxicities, and concurrent therapy was not recommended over sequential therapy due to the lack of improved benefit.[54]

The TORAVA study randomized patients 2:1:1 to receive first-line temsirolimus/bevacizumab, sunitinib, or bevacizumab/IFN-alfa. This phase II study demonstrated significant toxicity of the temsirolimus/bevacizumab combination, which caused 51% of patients in this treatment arm to discontinue treatment before progression was noted.[55] This finding caused the TORAVA investigators to conclude that this combination was not suitable for first-line treatment. A subsequent report from the TORAVA investigators suggested that the smaller randomized phase II setting may not be appropriate for comparisons of regimens such as these. In smaller studies, imbalances in the study arms that may not normalize through randomization make the final results uninterpretable.[56]

A phase II study of everolimus with bevacizumab showed activity in the first and second lines, with ORRs of 30% and 23%, respectively.[57] A phase III study of this combination is underway. In another trial, ~700 patients with TKI-refractory RCC will be treated with this combination. The anticipated completion date is March 2013. In addition, a randomized phase II trial is comparing bevacizumab/everolimus with bevacizumab/IFN-alfa as first-line therapy in mRCC.

Eastern Cooperative Oncology Group (ECOG) trial 2804 is a phase II study comparing different combinations of bevacizumab, temsirolimus, and sorafenib vs bevacizumab alone. Approximately 360 patients have been randomized into four arms: bevacizumab; bevacizumab/temsirolimus; bevacizumab/sorafenib; or temsirolimus/sorafenib. Results from this accrued study are anxiously anticipated.

VEGFR inhibitor + EGFR inhibitor: cediranib + gefitinib(Drug information on gefitinib) (Iressa)

Overexpression of EGFR has long been recognized in RCC.[58] Epidermal growth factor (EGF) is capable of stimulating proliferation of RCC both in vitro and in vivo. It also appears to be linked to tumorigenesis in von Hippel–Lindau (*VHL*)-mutant xenografts. Clinical trials of EGFR inhibitors such as erlotinib (Tarceva) have not shown impressive clinical activity, although in a prospective study of papillary RCC, an ORR of 11% was reported.[59] A phase II study of gefitinib was also initiated but has shown no responses. In the phase III setting, lapatinib (Tykerb) was shown to improve median OS in patients with cytokine-refractory disease compared with hormonal therapy (a historic control in RCC studies), with a shift from 37.9 to 46.0 weeks (HR, 0.69; $P = .02$).[60]

Some consideration has been given to whether EGFR inhibition alone is sufficient to impact tumor biology, given the modest effects of therapy. Combinations of EGFR inhibitors with VEGFR inhibitors have been attempted. In a phase I/II trial of sunitinib with gefitinib, investigators found the addition of gefitinib to be tolerable if the sunitinib dose was reduced to 37.5 mg. Of patients who received the maximum tolerated dose (MTD) of gefitinib (in combination with 37.5 mg of sunitinib), 37% experienced a PR while 34% had SD, for a clinical benefit rate of 71%.[61] With this combination, the DLT was diarrhea. An alternative approach using cediranib instead of sunitinib (ie, cediranib + gefitinib) has also been tested.[62] This regimen was also well tolerated, with diarrhea, anorexia, and fatigue being the most common adverse events. Of the 18 patients with RCC in this study, 6 achieved a PR.

Immunotherapy combinations

Given an unlikely toxic synergy, STIs have been tested in combination with immunotherapy approaches. The ROSORC trial randomly assigned treatment-naive patients to sorafenib with or without IL-2. Despite patients experiencing toxicity from IL-2 that required dose reduction, no benefit was detected for the addition as measured by PFS.[63] Similarly, a combination of sorafenib with the tumor necrosis factor (TNF)-alpha antagonist infliximab(Drug information on infliximab) (Remicade) resulted only in increased toxicity without improvement in response.[64] Combinations of sorafenib with low-dose IFN

also did not significantly impact outcome.[65] Another group tested recombinant interleukin-21 (rIL-21) with sunitinib, given preclinical data that rIL-21 sustained antitumor responses in engineered models of sunitinib resistance.[66] This combination resulted in excessive hematologic toxicity that prevented completion of the phase I study. A similar finding occurred with tremelimumab (CP-675206; an antibody against CTLA-4).[67] Rapid-onset acute renal failure was seen unexpectedly, preventing completion of the dose escalation.

Tolerable combinations include bevacizumab with IFN and temsirolimus with IFN.[68] However, the combination of temsirolimus with IFN, while tolerable, did not yield an improvement in OS in phase III evaluation.[53]

Perioperative Therapy

Perioperative systemic therapy has been shown in several clinical settings to impact clinical outcomes. Current practice guidelines do not include recommendations for adjuvant or neoadjuvant therapy. The earliest clinical studies defining the use of known active agents in this setting have not yet matured. Advances in this field have been largely limited by the lack of highly effective treatments with acceptable toxicity in the perioperative setting.

A formal exploration of the safety and feasibility of neoadjuvant VEGFR inhibition was reported for patients undergoing nephrectomy for RCC. All patients had clear-cell carcinoma and were eligible regardless of nodal status or metastases, provided they were deemed appropriate for nephrectomy. Using an alternative dosing scheme of 37.5 mg daily for 12 weeks, the investigators found no surgical complications in the sunitinib arm, with 85% of patients experiencing reduction in tumor size.[69] A similar experience was reported using sunitinib before nephron-sparing surgery for RCC.[70] Another study with short-course sorafenib showed partial responses without significant negative impact on the surgical procedure.[71] A fourth study using bevacizumab with or without erlotinib was conducted; wound dehiscence that was attributed to bevacizumab was noted.[72]

The use of STIs in the adjuvant setting has been and continues to be explored. Earlier studies in the adjuvant setting suffered from either a lack of effective treatments[73] or excessive toxicity from cytokines.[74] With the introduction of active targeted agents, a number of trials have emerged that have involved sorafenib (ASSURE), sunitinib (ASSURE, S-TRAC), pazopanib (PROTECT), and everolimus (EVEREST). Other trials are also in development with newer compounds. A positive impact on clinical outcomes holds potential for a significant advance in the clinical care of patients with advanced RCC, for whom the current standard of care calls for observation.

Cytoreductive Nephrectomy for Metastatic Disease

The traditional teaching in RCC has been that cytoreductive nephrectomy improves outcomes from systemic therapy. This teaching has been based on phase III data showing an improvement in response to IFN following nephrectomy in the metastatic setting.[75,76]

The generalizability of this statement to noncytokine therapies has been called into question. At this time, there are only limited data to guide practitioners. In a retrospective analysis of 314 patients beginning VEGFR-targeted therapy, cytoreductive nephrectomy did correlate with improved OS (19.8 vs 9.5 mo; HR, 0.44; $P < .01$).[77] However, the

REFERENCE GUIDE

Therapeutic Agents Mentioned in This Article

Aflibercept (VEGF Trap, AVE 005)
AAGS-003
AMG386
Axitinib (Inlyta)
Bevacizumab (Avastin)
BIBF 1120
BMS-936558 (MDX-1106, ONO-4538)
Cediranib (AZD2171)

same study showed that patients who underwent nephrectomy were younger, had better performance status, and tended to have fewer sites of disease.

The emergence of data in the perioperative setting demonstrating biological activity and safety calls for further investigation to determine the optimal timing or role of nephrectomy in the treatment of advanced disease.

Conclusions

As clinical data with cytokines, STIs, and immunomodulators become available, the therapeutic options for patients with RCC will only continue to grow. The multiplicity of options offers new hope for patients, but at the same time has led to a decrease in clinical trial participation, which is urgently needed to enable this field to advance. With so many promising agents, the inability to complete appropriately powered clinical studies threatens to stymie the rate of advancement in RCC clinical research. It has become more important now for treating physicians to be aware of areas of development so that patients appropriate for study can be identified.

Now more than ever, the potential for utilization of these therapies in concert with surgery and/or radiation therapy underscores the need for multidisciplinary teams centered on patients with RCC. In short, there are a number of promising treatments that appear to be active where currently available therapies are not. These include a series of TKIs against not only VEGFR and mTOR, but also FGFR and AKT. Additionally, the field of immunomodulation continues to evolve beyond cytokine therapy. This diversity of growth promises to continue to create opportunities for significant advancement toward a cure for this disease. At the current time, the sequential use of STIs that target the VEGF/VEGFR and mTOR pathways has the highest level of evidence for clinical practice. Integration of IL-2 into this paradigm requires an understanding of the risk/benefit ratio and the importance of patient selection. In the future, options for patients will ultimately derive from the performance of carefully designed clinical trials and the integration of comparative effectiveness research into the changing paradigm for this disease. As clinical investigators, we must contend with the limited pool of patients that exists. The small size of the patient pool stands in stark contrast to the large number of potential studies that could be performed to determine the comparative efficacy of emerging treatments. Thus, we must emphasize the need for collaborative networks to be organized to allow for efficient multicenter studies with clear clinical endpoints and aggressive biospecimen banking that will allow for translational research and advancement in this area. Given the complexity of such studies, partnerships between the pharmaceutical industry, academic institutions, and government regulators must be formed to lead these efforts. Ultimately, without aggressive and informative biospecimen interrogation, rationales for variations in the sequence or combination of therapies cannot be strongly hypothesis-driven. Emerging studies in the area of RCC demonstrate that scientific partnerships such as these that allow for translational research are possible, but care must be taken in deciding how to advance the next generation of agents into the clinical arena and determining in which settings they should be tested.

Dovitinib (TKI1258, CHIR-258)
Erlotinib (Tarceva)
Everolimus (Afinitor)
Foretinib (BSK136089, GSK089, XL880)
Gefitinib (Iressa)
High-dose Interleukin-2 (Proleukin)
IMA 901
Infliximab (Remicade)
Interferon-alfa
Interleukin-2
Ipilimumab (Yervoy)
Lapatinib (Tykerb)
Lenvatinib (E7080)
MK-2206
Pazopanib (Votrient)
Ramucirumab (IMC-1121B)
Regorafenib (BAY 73-4506)
Sorafenib (Nexavar)
Sunitinib (Sutent)
Temsirolimus (Torisel)
Tivozanib (AV-951, KRN-951)
Tremelimumab (CP-675206)

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

In summary, the field of RCC therapy is seeing a number of advances in current treatment paradigms. These include the introduction not only of newer and more potent drugs, but also of new molecular targets, new therapeutic strategies, and novel uses of existing treatments, all of which must be combined with aggressive research. For this field to continue to move forward, continued academic efforts must be supported.

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