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Translating Biology to Clinical Practice: Evolving Strategies for the Treatment of Renal Cell Carcinoma

A Review of a Satellite Symposium
Held in Conjunction With the 2008
American Society of Clinical Oncology
Genitourinary Cancers Symposium
February 15, 2008
San Francisco, California

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Statement of Need

Approximately 51,000 new cases of cancer of the kidney and renal pelvis were diagnosed in the United States in 2007. Patient prognosis varies considerably based on the stage of the disease at diagnosis. For patients who are diagnosed with local disease, 5-year survival rates reach almost 90%. Nephrectomy is the standard of care for local renal cell carcinoma (RCC). However, because RCC remains clinically silent for much of its natural history, 30% of patients present with metastatic disease. Another 30% of patients who have undergone apparent curative resection of their primary tumor develop metastases. Median survival for patients with advanced or metastatic disease is 6–12 months, with a 2-year survival rate of 10–20%.

For the past 20 years, cytokine therapy has been the mainstay of treatment for metastatic RCC, despite its toxicity, low response rate, and short survival benefit (only months). The potential for immunotherapy has been demonstrated with occasional spontaneous and dramatic remissions, but the poor outcomes experienced by the majority of patients with metastatic RCC underscore the need for more effective treatment. Because of an expanding understanding of the genetic and molecular basis of RCC, more than 80 new compounds are under development for treatment of advanced RCC. In particular, small molecules and monoclonal antibodies (MoAbs) that target and inhibit key signaling pathways involved in tumor growth, survival, and angiogenesis have demonstrated clinical benefit or are undergoing testing against standard cytokine therapy. This journal supplement will review the results obtained by current therapeutic strategies as a background to a detailed discussion of the clinical potential of current and emerging targeted agents for the treatment of RCC.

Target Audience

This activity is designed for oncologists, physicians, nurses, pharmacists, physician assistants, and other health care professionals interested in recent advances in the treatment of patients with RCC.

Educational Objectives

After participating in this educational activity, participants should be able to:

1. Describe the aberrant signaling pathways characteristic of RCC.
2. Discuss the safety and efficacy of recently approved novel multitargeted agents for metastatic RCC.
3. Discuss recent clinical trials investigating the safety and efficacy of MoAbs in the treatment of RCC.
4. Describe recent clinical trials investigating the safety and efficacy of novel agents targeting single pathways for the treatment of RCC.
5. Evaluate the potential clinical utility of prognostic and predictive factors in the treatment of RCC.

Method of Participation

This journal supplement is based on highlights from Translating Biology to Clinical Practice—Evolving Strategies for the Treatment of Renal Cell Carcinoma, an ancillary symposium, which utilized multiple methods of participation to engage attendees and enhance the learning process.

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Renal cell carcinoma (RCC) is the predominant form of kidney cancer, arising from the cells of the renal tubule. The prevalence of RCC has increased dramatically and continuously over the past five decades, rising by an estimated 125% over this period.[1] In 2007, an estimated 51,100 patients were newly diagnosed with RCC, and 12,900 died from the disease.[2] Improvements in imaging procedures have partially contributed to this rise in RCC diagnoses, but the increasing prevalence of risk factors—smoking, hypertension, obesity, and a changing diet—also may explain the dramatic increases.[3] After diagnosis patient survival is variable; based on 2004 statistics, the 5-year relative survival rate was approximately 62%.[4,5] However, patient survival is mainly dependent on the extent of the disease, as patients with locally confined tumors have an 80% better 5-year survival rate than those with metastatic disease (89.9% vs 9.1%, respectively). Because nearly 10–30% of patients present with metastatic RCC (mRCC), and many individuals progress to advanced RCC during treatment, a significant number of patients have a poor prognosis.

RCC can be classified pathologically by the cell type from which the tumor arose. The most common RCC histology is clear cell carcinoma, which comprises the majority of renal tumors. Non–clear cell histologies include papillary and chromophobe RCC.

The most commonly utilized staging system for RCC is the tumor, node, metastasis (TNM) system.[6] Using the TNM system, tumors classified as T1 or T2 are confined to the kidney. Classification as T3a signifies involvement of perinephric tissues or adrenal gland, whereas T3b and T3c denote venous involvement. T4 classification is associated with locally advanced progression. Positive nodal involvement is simply described by the number of infiltrated regional lymph nodes—N0, N1, or N2, the latter of which includes cases of at least two nodes. The presence or absence of distant metastasis is recorded as either M1 or M0, respectively. TNM staging is predictive of prognosis, and patients with the lowest stages have the best rates of 5-year survival (74–96%).[7]

The TNM system is also used when considering the proper course of therapy. The sole curative treatment for RCC is surgical resection, generally received by patients with localized disease. The gold-standard treatment for localized RCC is open nephrectomy, although there is increasing evidence that cytoreductive partial nephrectomy may be an option for select patients. Because disease recurrence is rare following successful surgical resection, adjuvant therapy is not currently recommended in these situations.

Conversely, few patients with advanced or mRCC benefit from surgery and systemic therapies are thus used to control the disease. For several years the mainstay systemic treatment was immunotherapy with cytokines such as interferon-alfa (IFNα) or interleukin-2 (IL-2). Although the exact mechanism of action for these agents is unclear, it is thought that the cytokines initiate an antitumor immune response that then triggers cancer cell death. Response to cytokine therapy varies greatly and most patients become refractory to treatment. This observation, combined with the large numbers of patients with poor prognosis as well as the increasing understanding of the biologic mechanisms underlying the disease, has focused much effort on the development of new therapies for RCC. These treatments, described below, are composed mainly of agents targeted at dysregulated proteins and pathways specific for RCC. These agents, both alone and in combination, may offer improved outcomes

for advanced RCC patients who otherwise have no treatment alternatives.

Prognostic Factors In Renal Cell Carcinoma: Current Status and Unanswered Questions

Christopher Wood, MD, Associate Professor of Urology and Cancer Biology at The University of Texas M. D. Anderson Cancer Center, discussed the latest findings in applying prognostic factors to assess RCC patients. Dr. Wood highlighted the benefits and drawbacks of several factors that have been investigated for their ability to predict patient risk, focusing on clinical studies in various RCC patient populations.

Current Risk Assessment Paradigms

Risk assessment is an essential consideration when determining the therapeutic options for RCC patients. By determining a patient's risk, the clinician can offer prognostic assessments for therapeutic interventions, as well as establish risk-based surveillance strategies to more effectively monitor the patient over time. Additionally, an accurate risk assessment may allow stratification of patients with local disease to receive adjuvant therapy clinical protocols and patients with metastatic carcinoma to be provided appropriate systemic therapeutic interventions.

The most widespread prognostic nomogram currently used in the clinic was developed at the Memorial Sloan-Kettering Cancer Center (MSKCC).[8] This nomogram uses five risk factors—low hemoglobin, high lactate dehydrogenase, high corrected calcium, the absence of a prior nephrectomy, and low Karnofsky performance status—to assess patient risk and prognostic benefit of therapy. Patients with three or more risk factors have the worst prognosis, while those with zero or one are the most likely to benefit from treatment. Other characteristics have also been evaluated for their prognostic potential.

Tumor Staging

Tumor staging is an important component of current risk assessment techniques, and advanced tumor stages have been clearly correlated with poor prognosis, regardless of therapy.[9,10] Using TNM staging guidelines, stage I patients have the best prognosis with a 5-year survival rate of 95%. Stage II and III patients have progressively worsening 5-year survival rates of 88% and 59%, respectively. The 5-year survival rate for patients with advanced stage IV disease is only 20%. A retrospective study of 286 RCC patients who had undergone radical nephrectomy additionally showed that the risk of developing mRCC was dependent on the stage of the disease at the time of surgery.[11] Because of these results, the authors of this study proposed patient surveillance protocols based on disease stage. Separately, a Canadian study found that RCC tumor stage can be predictive of both the rate of relapse and time to relapse after nephrectomy, as well as the site of relapse.[12] Significantly, the 5-year progression-free survival (PFS) rate in this study was 93% for pT1, 81% for pT2, 67% for pT3a, and 57% for pT3b (P<.001).

The tumor classification pT3a includes tumor invasion of sinus fat (SF) and/or perinephric fat (PF). Data from one study suggest that these distinct localizations of invasion can be used to further refine tumor staging as a prognostic indicator. In that study, patients with SF invasion were 63% more likely to die from RCC versus those patients with PF invasion (relative risk [RR], 1.63; 95% confidence interval [CI], 1.09–2.46; P=.018).[13] Conversely, a recent comparison between the SF and PF patient subgroups found no significant difference in 5-year cancer-specific survival (50.8% vs 54.1%, respectively).[14] Additionally, the presence of SF invasion did not significantly predict 5-year cancer-specific survival compared to the absence of SF invasion (53% vs 50%, respectively). Based on these findings, additional subgroup stratification of pT3a patients according to location of fat invasion is not of prognostic importance.

Alternatively, subgroup classification of stage pT3b disease does have prognostic significance. Tumors classified as pT3b are characterized as having venous invasion, either renal vein thrombi or vena cava thrombi below the level of the diaphragm.[15] Compared with pT3a, patients with pT3b disease have a significantly worse prognosis (median 5-year cancer-specific survival 77% vs 62%, respectively; P=.008).[16] However, the prognostic importance of concomitant venous tumor invasion and extrarenal tumor extension (ERE) is not addressed by the pT3 tumor classification. To resolve this, a study recently assessed the survival of patients with either or both of these features.[16] When patients with venous tumor thrombus (VTT) only or ERE only were compared, no significant difference in median 5-year cancer-specific survival following surgery was observed (77% vs 79%, respectively). However, patients having both VTT and ERE had a significantly poorer outcome (5-year cancer-specific survival 54%) than patients with either VTT or ERE alone (P<.001). Therefore, subclassification of pT3b patients according to the presence of VTT and ERE, either alone or together, can improve risk assessment for these patients.

Further refinement of RCC tumor staging can be achieved by including the extent of nodal involvement. A study of over 1,600 patients at the Mayo Clinic determined that the extent of regional lymph node involvement at the time of nephrectomy was significantly associated with cancer-specific survival.[17] The estimated cancer-specific 1-year survival rate for patients with pN0 or pNX

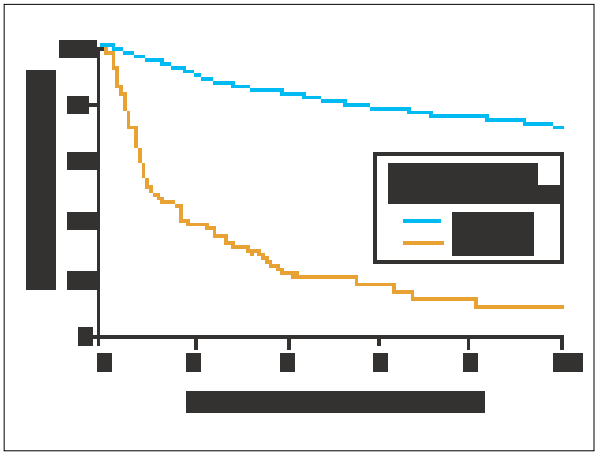

Figure 1. Influence of nodal involvement on outcome following surgery for localized renal cell carcinoma.

Data from Blute ML et al.[17]

clear cell RCC was 95.5%, compared with only 52.2% for patients with either pN1 or pN2 clear cell RCC (Figure 1). The difference in survival became even more dramatic at 10 years (72.5% vs 11.4%, respectively). This difference equated to a significantly increased risk of death for patients with regional lymph node involvement (risk ratio, 7.87; 95% CI, 5.98–10.36; *P*<.001). These findings were further extended to the mRCC setting with a recent study of 429 patients with metastatic disease (M1) who were either node-positive or -negative.[18] Patients with metastatic disease but no nodal involvement (N0M1) displayed the best prognosis, with a median disease-specific survival (DSS) of 24.6 months, whereas patients with unresectable N1M1 or N2M1 disease had the worst prognosis (median DSS 4.9 months; *P*<.00001). Interestingly, if the involved lymph nodes could be successfully removed, the median DSS for these patients improved to 16.3 months.

Although the TNM staging system differentiates between nodal-positive patients with involvement of one or more than one node (N1 or N2, respectively), recent evidence suggests that this subset stratification is not an important determinant of outcome. An analysis of N1 and N2 patients following surgery showed no significant difference in the estimated median 5-year cancer-specific survival between the two groups (39% vs 18%, respectively; *P*=.0912).[19] However, both groups had significantly decreased survival compared with an estimated 83% probability of the N0/NX combined subgroups (*P*<.001 for both comparisons). Because no difference was noted between the N1 and N2 groups, it seems unnecessary to substratify nodal status.

Tumor Grade

The Fuhrman nuclear grade of the tumor is another well-established prognostic indicator for RCC.[20,21] This tumor grading scheme is based on nuclear size and shape, along with the prominence of the nucleoli. Increasing Fuhrman grades of I, II, III, and IV are associated with median 5-year cancer-specific survival rates of 94%, 86%, 59%, and 31%, respectively.[22]

Tumor Histology

Several distinct renal tumor histologies have been identified, including benign oncocytomas, clear cell RCC, and non–clear cell tumors such as papillary and chromophobe RCC. Patients with localized disease and a non–clear cell histology have a superior prognosis compared with those having clear cell RCC.[23] However, once the tumor metastasizes, non–clear cell histologies are associated with a much poorer prognosis.[24] Two studies clearly showed this following therapeutic intervention. In the first, patients with non–clear cell histologies had a significantly decreased probability of survival after interferon therapy compared with those with clear cell RCC (RR, 0.44; 95% CI, 0.24–0.8; *P*=.006).[25] In the second study, the median DSS for patients with non–clear cell histologies undergoing cytoreductive surgery was significantly worse than for patients with clear cell disease (9.7 vs 20.3 months, respectively; *P*=.0003).[26] Additionally, patients with non–clear cell RCC were more likely to have nodal metastases (*P*<.001). Although it seems that a clear "switch" in tumor biology occurs in the progression from localized to metastatic disease which affects prognosis, the relative rarity of non–clear cell disease may impact these observations. Because of this, most nomograms either do not account for histology or only consider clear cell histology for analysis.

The conventional thought that RCC histology is not important for determining prognosis was recently challenged by the results of a study designed to investigate the aggressive switch from localized to metastatic disease in papillary RCC.[27] As was previously observed with localized RCC, those patients with papillary histology had a significantly superior median 5-year cancer-specific survival rate versus patients with clear cell histology (88% vs 81%; *P*=.035). Conversely, for individuals with metastatic RCC, having a papillary histology was associated with a significantly worse median 5-year cancer-specific survival rate (0% vs 29%; *P*=.005). Interestingly, when patients with localized disease were additionally categorized according to TNM stage, the difference in median 5-year cancer-specific survival lost statistical significance for lower-stage tumors (Figure 2). However, patients with localized T3b-cN0/NXM0 RCC and papillary histology did have a significantly poorer prognosis com-

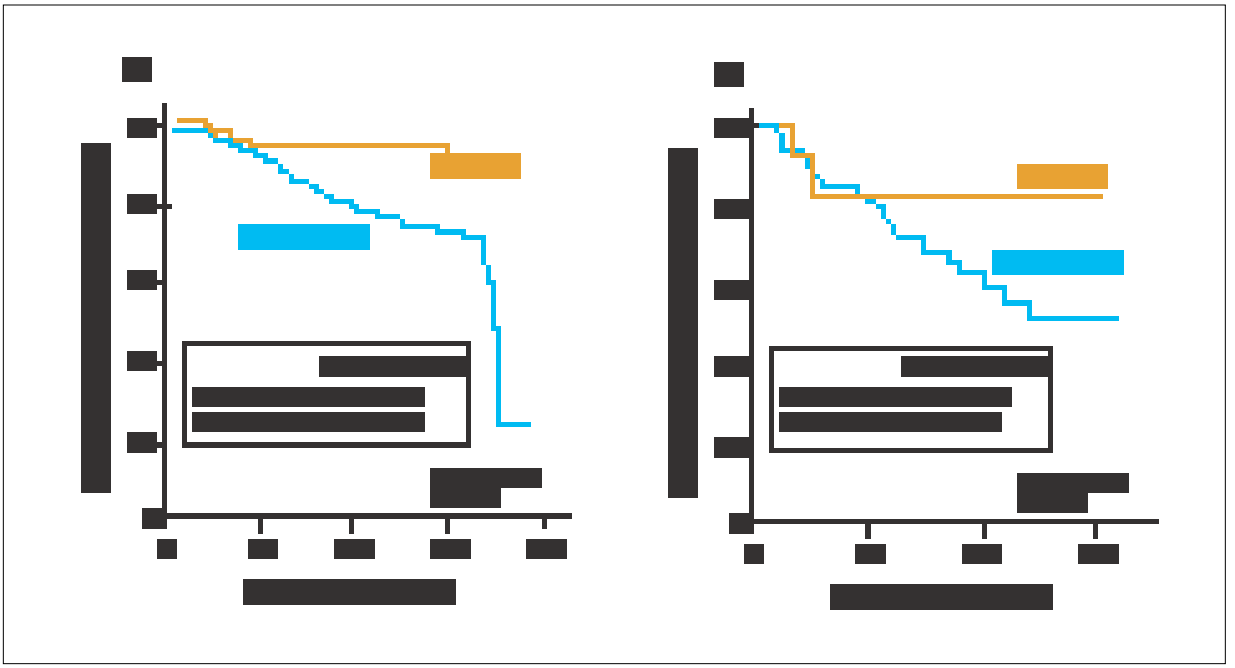

Figure 2. Cancer-specific survival (CSS) probability. A) 1,127 patients surgically treated for T1-2N0/NxM0 RCC; B) 199 patients surgically treated for T3aN0/NxM0 RCC stratified according to the histologic subtype.

pared to patients with clear cell histology (median 5-year cancer-specific survival 35% vs 66%, respectively; *P*=.012). Nodal involvement (TanyN1-2M0 RCC) significantly affected prognosis, as node-positive patients with papillary histology had a superior median 5-year cancer-specific survival than those with node-positive clear cell histology (65% vs 19%; *P*=.029). As a result of this study, it is now understood that vascular and nodal invasions have dramatically different effects on the prognosis of clear cell and papillary histologies. Vascular invasion significantly lowers the prognosis for patients with papillary RCC compared to patients with clear cell RCC and, conversely, nodal invasion reduces the prognosis for individuals with clear cell histology compared with those with papillary histology.

Microvascular Invasion

Recently a study of 230 RCC patients found that microvascular invasion, as well as tumor size and grade, were strong and independent prognostic factors for predicting survival.[28] A retrospective review of these patients showed that microvascular invasion could highly predict patient outcome. Median 5-year disease-free survival for patients with no evidence of microvascular invasion was significantly higher compared with patients who had microvascular invasion (87.1% vs 27.2%; *P*<.001). This translated into higher cancer-specific survival as well (88% vs 39.7%; *P*<.001). Other studies have reported a similar prognostic importance for microvascular invasion.[29,30]

Lymphocyte Infiltration

Increased lymphocytic infiltration of RCC has been found to be independently associated with cancer-specific death (RR, 2.62; *P*<.001).[31] A recent asessment of 170 patients who had undergone nephrectomy for clear cell RCC further confirmed this by testing for the presence of T cells in tumor specimens.[32] Patients with CD4- and CD25-positive T cells that were also positive for transcription factor Foxp3 exhibited the poorest prognosis and cancer-specific survival, while those with Foxp3-negative T cells had a better outcome.

Tumor Size

Tumor size may also be a useful predictor for both local and locally advanced RCC. One study of 706 patients with pT2 RCC showed a significant association between tumor size and DSS (hazard ratio [HR], 1.11; *P*<.001).[33] Using 11 cm as a cut-off to stratify patients according to tumor size, this study found a significant difference in the DSS of the two groups of patients. The 5-year DSS for patients with tumors no more than 11 cm was 73% versus 57% for patients with tumors greater than 11 cm (*P*<.0001). Additionally, patients with larger tumors were

more likely to suffer from metastatic disease, although Fuhrman grade and histologic subtypes were similar between the two groups.

Presence of Symptoms

Survival was also significantly associated with clinical presentation, especially if the patient was symptomatic at diagnosis, in a retrospective study of 230 RCC patients.[34] The median 5-year disease-free survival rates for symptomatic and asymptomatic patients were 57.3% and 82.9%, respectively (P<.001). Similarly, the median 5-year cancer-specific survival rates for these patients were 64.1% and 85.2%, respectively (P<.001). This finding is especially important in light of the fact that the diagnosis of asymptomatic RCC has dramatically increased over the past three decades because of improved diagnostic and screening tests.

Cachexia also significantly predicted outcome in patients with T1 RCC.[35] After controlling for tumor size, grade, and performance status, cachexia was found to predict significantly worse relapse-free survival (HR, 3.03; P=.032) and DSS (HR, 4.39; P=.011).

Molecular Markers

A variety of tissue and serum markers have been demonstrated to have prognostic potential in small institutional studies; however, these need to be validated in larger trials. These markers include the presence of thrombocytosis, C-reactive protein, transforming growth factor β, and circulating cells positive for cytokeratins, carbonic anhydrase IX (CAIX), or cadherin 6. Immunologic markers that have shown evidence of prognostic capability include B7H1 and B7H4, as well as PD-1. CAIX, phosphatase and tensin homolog (PTEN), CAXII, and EpCam have all been associated with improved survival, whereas increased expression of Ki67, vimentin, gelsolin, and the tumor suppressor p53 are all correlated with decreased survival.[36]

In a recent clinical study, expression of p21, a cell cycle regulatory protein, was found to offer opposing prognoses dependent on the disease stage.[37] After immunohistochemical analysis of 366 RCC patients, high levels of nuclear p21 in localized disease was correlated with a better prognosis. Conversely, high levels of both nuclear and cytoplasmic p21 in metastatic disease were associated with a worse outcome. A major implication of this study is the finding that p21 may play a role in the biologic conversion of the tumor from local to metastatic.

Applying Current Risk Assessments to Patient Selection for Adjuvant Trials

One of the goals of risk assessment is to determine which patients would most benefit from certain adjuvant therapies. However, selection of patients solely on tumor stage and grade may not be stringent enough criteria to observe a therapeutic benefit. A recent example of this potential problem was noted in a randomized clinical trial investigating the heat shock protein gp96–based vaccine vitespen.[38] In this study, 728 eligible RCC patients underwent nephrectomy, followed by stratification based on tumor stage and grade. Those patients deemed as having a high risk of relapse were randomized to receive either observation alone or vitespen therapy. Initially, early analysis showed no statistically significant difference between the two treatment arms in either relapse-free survival or overall survival (OS). However, a subset analysis which categorized patients according to disease stage revealed patients with earlier stage disease (T1, T2, T3a) did derive a benefit from vitespen therapy (HR, 0.570; P=.052). Alarmingly, patients with more advanced stage disease (T3b) who received vitespen actually had worse relapse-free survival (HR, 1.868; 95% CI, 0.999–3.494) and OS (HR, 3.279; 95% CI, 0.841–12.78). A likely explanation for these data is that patient stratification according to tumor stage and grade alone did not sufficiently differentiate important differences between the two treatment groups.

Future Refinements in Risk Assessment

Current research is focused on correlating gene expression with prognosis in RCC patients. It has recently been shown that renal tumors have distinct genetic profiles that may be able to be used in risk assessment analysis.[39,40] Several studies have determined that the various histologic subtypes of RCC can be distinguished using gene expression profiling.[41-44] This finding supports the idea that each histology has a distinctive biology, which could explain why different histologies have varying prognoses.

A study of 29 clear cell RCC cases reported that unsupervised clustering revealed two distinct patient subgroups with differing 5-year cancer-specific survival prognoses.[45] Approximately 40 genes were found to be important in segregation of these two groups. This report was followed by a larger study of patients with stage IV RCC.[46] In this key study, a 45-gene signature was identified that could predict poor patient outcome. Future studies will further test the prognostic predictive ability of microarray analysis in larger cohorts of patients.[47]

Another technique currently in preclinical testing is difference gel electrophoresis, an assay that allows for detection of differential protein expression between malignant and normal kidney tissue from the same patient. This application has already been used to show differential protein expression in a multitude of tumor types.[48-51]

Table 1. Receptor Tyrosine Kinase Inhibitors Inhibiting Vascular Endothelial Growth Factor Receptors (VEGFRs) and Platelet-derived Growth Factor Receptors (PDGFRs)

	Target						
Inhibitor	**VEGFR1**	**VEGFR2**	**VEGFR3**	**PDGFR**	**c-Kit**	**FGFR**	**Other**
Cediranib	+	+	+				
Pazopanib	+	+	+				
Sunitinib	+	+	+	+	+	+	
Axitinib	+	+	+	+	+	–	
Sorafenib	±	+	+	+			RAF
Vandetanib	–	+	–	–			EGFR
Vatalanib	+	+	+	+	+		
XL647		–	+	_			
XL999		+	+	+	+	+	

EGFR=epidermal growth factor receptor; FGFR=fibroblast growth factor receptor.

Multitargeted Tyrosine Kinase Inhibitors: Newly Approved Therapies for RCC and Their Effect on the Standard of Care

Ronald Bukowski, MD, Emeritus Staff Consultant at the Cleveland Clinic Taussig Cancer Center and Professor of Medicine at CCF Lerner College of Medicine at Case Western Reserve University, presented a comprehensive review of the multitargeted tyrosine kinase inhibitors (TKIs) that have received approval or are under investigation for RCC. After summarizing the pivotal clinical studies, Dr. Bukowski discussed how these agents have changed the standard of care for both treatment-naive and -refractory patients.

Currently Approved Multitargeted TKIs

The multitargeted TKIs are a novel class of small molecule compounds which inhibit a wide variety of receptor tyrosine kinases. The most common targets of this drug class include the vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), and epidermal growth factor receptors (EGFRs). However, each agent inhibits multiple tyrosine kinases to various degrees (Table 1). For example, although both sunitinib and sorafenib inhibit VEGFR and PDGFR, sunitinib, unlike sorafenib, is also able to inhibit the tyrosine kinases c-Kit and fibroblast growth factor receptor. Conversely, only sorafenib is capable of inhibiting the serine/threonine kinase Raf. To date, significant clinical activity in RCC has been attributed to a number of these inhibitors, especially those which inhibit VEGFR and PDGFR, and sunitinib and sorafenib have both received US Food and Drug Administration (FDA) approval for use in mRCC.[52] Together these agents have altered the standard treatment paradigm for patients with mRCC.[53]

TKIs in Treatment-Naive Patients

The efficacy of sunitinib in untreated mRCC patients was established in a key multicenter study.[54] This phase III clinical trial randomized 750 patients to receive either sunitinib or IFNα, with a primary endpoint of PFS. Enrolled patients had measurable disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Sunitinib-treated patients more than doubled their median PFS compared with those treated with IFNα (11 vs 5 months, respectively), which corresponded to a hazard ratio of 0.42 (95% CI, 0.32–0.54; *P*<.001; Figure 3). Remarkably, after patients were stratified according to MSKCC prognostic criteria, sunitinib remained superior to IFNα across all risk categories. The median PFS for the low-risk sunitinib group was not reached and was 11 and 4 months for the intermediate- and high-risk groups, respectively, as compared to 8, 4, and 1 months, respectively, in the IFNα arm. Additionally, sunitinib treatment was largely beneficial compared with IFNα across several other patient risk subgroups, including prior nephrectomy, ECOG status, and time since diagnosis. Sunitinib treatment also led to a superior objective response (OR) rate compared with IFNα (31% vs 6%, respectively, *P*<.001). These findings support the use of sunitinib as first-line therapy for mRCC patients over other standard therapies.

Recently, a phase II trial evaluating sorafenib in treatment-naive mRCC patients was completed.[55] In this study, patients were randomized to receive either sorafenib

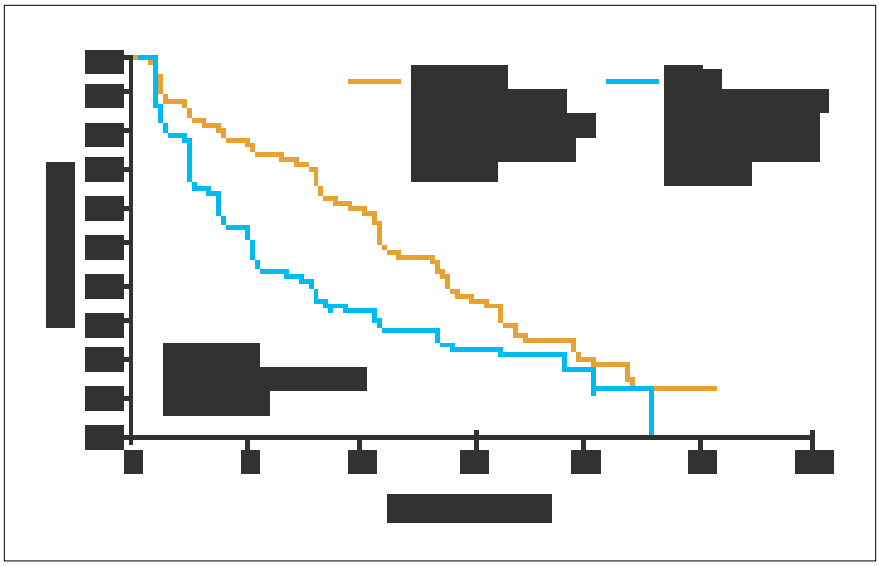

Figure 3. Sunitinib versus IFNa in first-line mRCC: PFS.

Data from Motzer et al. *J Clin Oncol.* 2007;250(18S pt 1): Abstract 5024.

CI=confidence interval; CR=complete response; HR=hazard ratio, IFN=interferon; mRCC=metastatic renal cell carcinoma; ORR=overall response rate; PFS=progression-free survival; SD=stable disease.

or IFNα therapy. There was no significant difference in median PFS between the two treatment arms (5.7 vs 5.6 months, respectively). Sorafenib produced similar clinical benefit compared with IFNα, with little change in the number of patients achieving a complete response (CR), partial response (PR), or stable disease (SD). However, individual treatment-naive patients may respond to sorafenib, and many experience at least long-term SD.

TKIs in Treatment-Refractory Patients

The TARGET trial was a double-blind, placebo-controlled phase III study which enrolled patients with mRCC that was progressing on standard therapy.[56] A total of 903 patients received either placebo or continuous sorafenib treatment on a randomized basis. An assessment of median PFS showed that sorafenib was superior to placebo (5.5 vs 2.8 months, respectively). The sorafenib group had a HR of 0.44 for disease progression (95% CI, 0.35–0.55; *P*<.01). Sorafenib also produced superior clinical benefit over placebo in these patients, although the best responses achieved were PRs (10% vs 2%, respectively; *P*<.001). Because of these promising results, the trial was amended to allow patients in the placebo arm to cross over to the sorafenib arm. This early crossover affected the analysis of OS, but when this was corrected for, the median OS was also superior for sorafenib-treated patients compared to placebo-treated patients (17.8 vs 14.3 months, respectively; *P*=.0287).[57] This trial was the key determinant in the approval of sorafenib for advanced mRCC.

The accelerated approval of sunitinib for mRCC was based on the results of two independent single-arm multicenter phase II trials.[58,59] All patients had mRCC and had previously failed cytokine therapy. The first trial (N=63) allowed any mRCC histology, and the second trial (N=105) evaluated individuals with clear-cell histology and prior nephrectomy. An analysis of the pooled data shows the OR rate for these patients was 45%, with the majority having either PR (12%) or SD (32%).[60] Interestingly, many of those patients who were classified as having SD still experienced tumor regression, although not to enough of a degree to be considered a PR.

Novel Kinase Inhibitors Under Investigation

Several novel TKIs are under active investigation in clinical studies for mRCC, including axitinib, pazopanib, and cediranib. The primary target of each of these agents is thought to be VEGFR. Preliminary studies of axitinib are especially exciting, showing axitinib to be active in both cytokine-refractory (CR + PR: 44%) and sorafenib-refractory (CR + PR: 21%) mRCC.[61] Additionally, a study in 225 patients shows pazopanib produces a 27% CR + PR rate.[62] Finally, cediranib treatment results in a 37% rate of CR plus PR.[63,64]

Inhibitors of EGFR show more limited success in mRCC, with the exception of lapatinib, which is also an inhibitor of the HER2 receptor. In a randomized phase III trial of 417 mRCC patients who had EGFR-positive tumors, the efficacy of lapatinib was compared with hormonal therapy.[65] Although there was no significant difference in efficacy when all patients were analyzed together, lapatinib was superior to hormonal therapy when only patients with high EGFR expression were considered. In these patients, the median OS in the lapatinib group was 46 weeks, compared with 37.9 weeks in the hormonal therapy group (*P*=.02).

Multitargeted Kinase Inhibitor—Impact on Standard Treatment Paradigms

The introduction of multitargeted kinase inhibitors has had a dramatic impact on the treatment of patients with mRCC. The current standard of care for first-line therapy for good- to intermediate-risk patients is sunitinib. Additionally, IFNα and bevacizumab are also useful in this setting, as is high-dose IL-2 therapy. For treatment-naive patients with a poor risk assessment the preferred frontline therapy is temsirolimus, although sunitinib is beneficial for these patients as well. Sorafenib has been established as the treatment of choice for patients with cytokine-refractory disease, and there is evidence that sunitinib and bevacizumab may also be active in these patients. Currently, novel agents are under investigation for their benefit in the setting of VEGFR inhibitor–refractory or mammalian target of rapamycin (mTOR) inhibitor–refractory mRCC. Until the efficacy of these agents can be established, one alternative is to administer sequential TKIs as maintenance therapy, changing agents when disease progression is observed.

Targeting mTOR Signaling: A Novel Treatment Strategy for Metastatic Renal Cell Carcinoma

David Quinn, MD, PhD, FRACP, Associate Professor of Medicine at the Keck School of Medicine, Chief of the Genitourinary Medical Oncology Section and Medical Director at the Kenneth J. Norris Comprehensive Cancer Center at the University of Southern California, presented evidence of the importance of mTOR signaling in renal cancer. After discussing the rationale behind targeting mTOR in RCC, Dr. Quinn highlighted the recent clinical research in this area.

mTOR Signaling in RCC

Hyperactivation of the mTOR pathway is a common feature in numerous tumors, including many RCCs.[66] The activity of mTOR is positively regulated by upstream kinases, including phosphoinositol 3-kinase and Akt, both of which have been shown to be over activated in several tumor types. The PTEN protein normally negatively regulates Akt activity, thereby decreasing mTOR activation, and is therefore considered a tumor suppressor. However, PTEN is often inactivated in tumors, serving as another source of upregulation of mTOR activation. mTOR is a protein kinase, which when activated goes on to phosphorylate and activate several downstream substrates. The consequences of mTOR activation are increased translation of proteins involved in cell survival, proliferation, and angiogenesis, thereby conferring a survival benefit to these cells.[67]

mTOR was first discovered as the cellular target of its namesake drug, rapamycin. Since then several lines of evidence have argued for the importance of targeting this pathway in RCC. Activation of the mTOR pathway was recently shown to be significantly correlated with pathologic features as well as survival of RCC patients.[68] Clear cell and high-grade tumors carried the most significant alterations in the mTOR pathway, as did those tumors with poor prognosis. Among the components involved in mTOR signaling, PTEN expression and phosphorylation of the S6 kinase were the most strongly associated biomarkers. Separately, primary RCC tumors from tuberous sclerosis patients, who harbor loss-of-function mutations in the mTOR-inhibitory proteins TSC1 and TSC2, were found to express elevated levels of activated mTOR and downstream effectors of mTOR.[69] In another study, mutations in the tumor suppressor PTEN, a negative regulator of Akt signaling, were associated with increased mTOR activation.[70] Additionally, mouse models of RCC have demonstrated that rapamycin could effectively inhibit tumor progression and metastatic growth.[71,72]

mTOR Inhibitors in Clinical Trials

Although a potent inhibitor of mTOR, rapamycin has low solubility and is unstable in solution; therefore, it is not a good candidate for parenteral administration.[73] As a result, the mTOR inhibitors which have been investigated in advanced clinical trials are analogs of rapamycin, designed to have more beneficial pharmacologic properties while still retaining high affinity for the mTOR protein. Temsirolimus is a soluble rapamycin ester that was recently approved for treatment of advanced RCC.[74] Temsirolimus was designed for weekly intravenous administration. The rapamycin derivative everolimus has also shown significant benefit in patients with RCC.[75] Everolimus can be delivered orally daily or weekly. The non-prodrug rapamycin analog deforolimus (AP23573), which has recently entered clinical trials, is given through daily dosing.[76]

The results of a phase III international multicenter study comparing front-line temsirolimus with IFNα were recently reported.[77] This trial randomized 626 patients to three treatment arms: temsirolimus, IFNα, or both drugs together. Patients had advanced mRCC with poor prognosis, (ie, ≥3 factors which predicted high-risk disease). The median PFS in patients who received temsirolimus alone was twice that of those receiving IFNα alone (3.8 vs 1.9 months, respectively; P=.0001), and combination therapy did not extend PFS any further (median PFS=3.7 months). OS was also statistically superior in the temsirolimus arm versus the IFNα arm (10.9 vs 7.3 months, respectively; P=.0069; Figure 4). This corresponded to a HR of 0.73 (95% CI, 0.58–0.92; P=.008). Importantly,

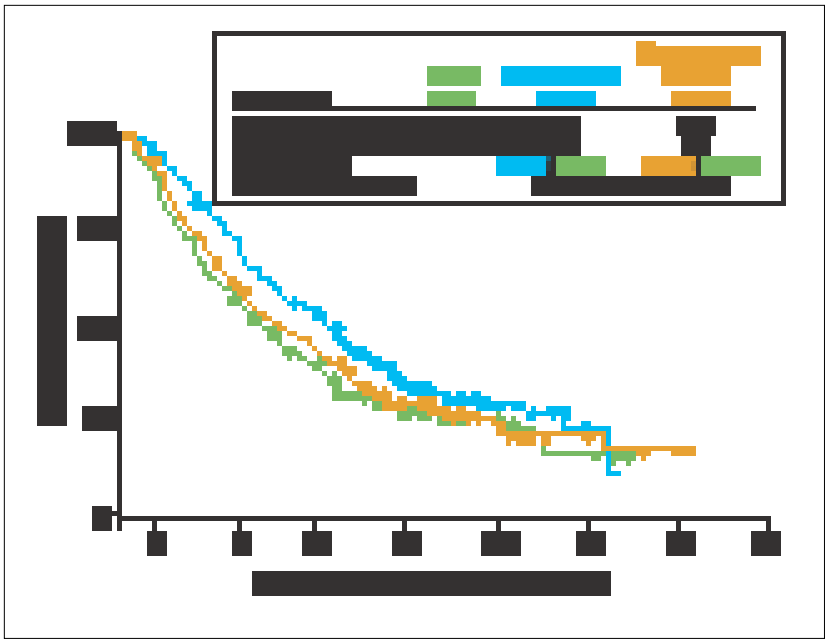

Figure 4. Temsirolimus versus IFNα in first-line, poor-risk mRCC: OS.

Data from Hudes at al.[77]

IFN=interferon; mRCC=metastatic renal cell carcinoma; OS=overall survival.

the combination arm did not derive a statistically significant benefit in OS compared with the IFNα-alone arm (8.4 vs 7.3 months, respectively). Although the OR rate did not differ significantly between each treatment group (4.8%, 8.6%, and 8.1% for IFNα, temsirolimus, and the combination), when the proportion of patients who had SD for at least 6 months was considered, temsirolimus therapy offered a clear benefit. The OR plus SD rate for IFNα alone was 15.5%, compared with 32.1% for temsirolimus only (P<.001) and 28.1% in the combination group (P=.002). In this study, fewer patients in the temsirolimus arm compared with the IFNα arm experienced serious adverse events (67% vs 78%, respectively: P=.02). Adverse events that were more frequently reported in the temsirolimus group included rash (47%), stomatitis (20%), and various metabolic abnormalities such as hyperlipidemia (27%), hyperglycemia (26%), and hypercholesterolemia (24%). Although these adverse events can be a particular problem in older patients, they respond well to standard therapy.

The efficacy and safety of everolimus in mRCC was investigated in a single-arm phase II trial of 37 treatment-refractory patients.[78] This study showed a median PFS of 11.17 months and median OS of 24.17 months for these individuals with advanced disease. Importantly, 32% displayed a PR, and 38% exhibited SD. The remaining 30% had evidence of progressive disease. It was further shown that approximately 70% of patients had tumor shrinkage, which was ≥10% in 50% of these individuals. Pneumonitis was the most frequently reported grade 2 or 3 adverse event following everolimus therapy, although other grade 2 events, including rash and stomatitis, occurred. Based on these promising phase II data, a larger phase III trial is now open and accruing patients. This trial will assign individuals with previously treated mRCC to receive either everolimus or placebo on a randomized basis.

As mTOR inhibitors continue to be studied in the clinical setting, several questions regarding their administration remain. For example, the optimal dosage and sequencing schedules in RCC for each of the three mTOR inhibitors need to be determined. Additionally, the use of these inhibitors as salvage therapy following tyrosine kinase agents such as sorafenib and sunitinib still is unknown. Finally, the role of mTOR inhibitors as first-line or second-line therapy needs to be established, in order to allow the best use of these drugs in either setting.

Predictors of Response to mTOR Inhibitors

A post hoc analysis of the phase III temsirolimus trial described above was performed to determine if any factors could be determined to be predictive of response to temsirolimus.[79] This analysis only included data from patients in the single-agent arms (IFNα alone or temsirolimus alone). Response to temsirolimus seemed to be affected by tumor histology, as the reduction in the hazard ratio for OS in non–clear-cell RCC was much greater than that for clear-cell RCC (HR, 0.55 vs 0.85, respectively). The same was also observed for PFS (HR, 0.36 vs 0.84, respectively). The authors of this study speculated that the reason why patients with non–clear-cell RCC showed greater benefit with temsirolimus could be due to the fact that cytokines, including IFNα, are known to be less

active in non–clear-cell RCC. Age also played an important role in determining treatment response, as patients under 65 years had greater reductions in hazard ratios for OS and PFS compared with individuals at least 65 years of age (OS HR, 0.67 vs 1.15, respectively; PFS HR, 0.69 vs 1.00, respectively). In this study, 117 patients were categorized as having intermediate-risk disease and most patients had poor risk, those with the worst prognoses seemed to fare better in terms of OS with temsirolimus treatment than those with better prognoses (HR, 0.70 vs 1.17, respectively).

A recent report suggested that certain biomarkers may be predictive of response to temsirolimus for RCC patients.[80] Immunohistochemical examination of tissue from 20 patients who had received temsirolimus discovered that phosphorylation of S6 kinase, an indication of mTOR activity, was predictive of response to temsirolimus (P=.02). There was also a correlation between expression of phosphorylated (activated) Akt and temsirolimus response, although it was not statistically significant. In each case, no patient without high expression of either of these two phosphorylated proteins experienced a response to temsirolimus. These data suggest that it may be possible to use these proteins as biomarkers to select RCC patients who would most benefit from temsirolimus therapy, a finding undergoing further clinical investigation.

Monoclonal Antibody Blockade of the VEGF Pathway: An Emerging Option for the Management of RCC

Thomas Hutson, DO, PharmD, FACP, is Director of the Genitourinary Oncology Program for Texas Oncology, at the Charles A. Sammons Cancer Center at Baylor University, and Co-Chair of genitourinary research for US Oncology. Dr. Hutson spoke about why VEGF is an appropriate target in mRCC and discussed the results of clinical trials evaluating VEGF pathway blockers.

Rationale for Targeting VEGF in Metastatic Renal Cell Carcinoma

RCC tumors are noted to have a high degree of vascularization, mainly due to dysregulation of molecular pathways important in angiogenesis.[81] One of the most strikingly common genetic abnormalities in RCC is loss of function of the von Hippel-Lindau (VHL) protein.[82] This early event in the formation of clear cell RCC is one of the most common causes of inherited clear cell RCC, and accounts for nearly 75% of sporadic clear cell RCC.[82,83] In up to 60% of RCC cases, loss of VHL function occurs. Either mutation of the *VHL* gene or epigenetic alterations, including methylation of the *VHL* gene promoter, are responsible for another 10–20% of RCC tumors.[84] The VHL protein participates in several growth and survival regulatory signaling pathways. Most notable among these is the hypoxia-inducible pathway, which is triggered under conditions of low oxygen tension. When present, VHL functions with elongin B and C, RING-box protein 1, and other proteins to form an ubiquitin-protein ligase complex. Under normal oxygen conditions, this VHL complex binds with and polyubiquitinates hypoxia-inducible factor (HIF)-1α, targeting it for proteasomal degradation.[85] However, in the absence of VHL, HIF-1α is not degraded, allowing HIF-1α to bind with its partner, HIF-1β, and translocate to the nucleus where it functions as a transcription factor for genes with hypoxia response elements within their promoter. Two of these genes encode the growth factors VEGF and PDGF, and upregulation of their transcription leads to their increased production and ability to activate their respective receptors.[86,87] The consequences of VEGF- and PDGF-triggered signaling is cell survival and proliferation, better resistance to hypoxic conditions, and increased angiogenesis; the latter gives rise to the vascular phenotype typically associated with RCC. Additionally, HIF-1α stimulates the expression of three transcriptional repressors of E-cadherin, thereby promoting tumor metastasis.[88,89] Production of the HIF-1α protein is controlled by mTOR.[90] The mTOR signaling pathway is itself upregulated in a number of RCC cases, causing overproduction of HIF-1α, which, when coupled with loss of VHL-mediated degradation, leads to accumulation of this oncogenic transcription factor.

The VEGF family includes five members: VEGF-A, -B, -C, and -D, and placental growth factor.[91] Of these, VEGF-A is most often exploited for therapeutic intervention. VEGF exerts its function through binding to VEGFR, of which three forms have been identified. This binding elicits different cellular responses including angiogenesis and lymphatic angiogenesis. VEGF has been suggested to be a useful prognostic indicator for estimating prognosis of RCC patients, and recent evidence has also shown it is predictive of survival following therapy.[92] High levels of circulating VEGF in the serum of RCC patients have been correlated with poor survival following cytokine therapy.[93] The same has also recently been shown in patients receiving TKI therapy. An analysis of RCC patients receiving sorafenib found that high levels of VEGF (>131 pg/L) were predictive of a worse PFS rate compared with low levels of VEGF (≤131 pg/L).[57] The median PFS of patients in each group was 2.7 versus 3.3 months, respectively, corresponding to a hazard ratio of 1.44 (95% CI, 1.13–1.85; P< 0.01; Figure 5).

Several therapeutic strategies have been implemented to target VEGF, leading to inhibition of endothelial cell growth and angiogenesis, two of which were

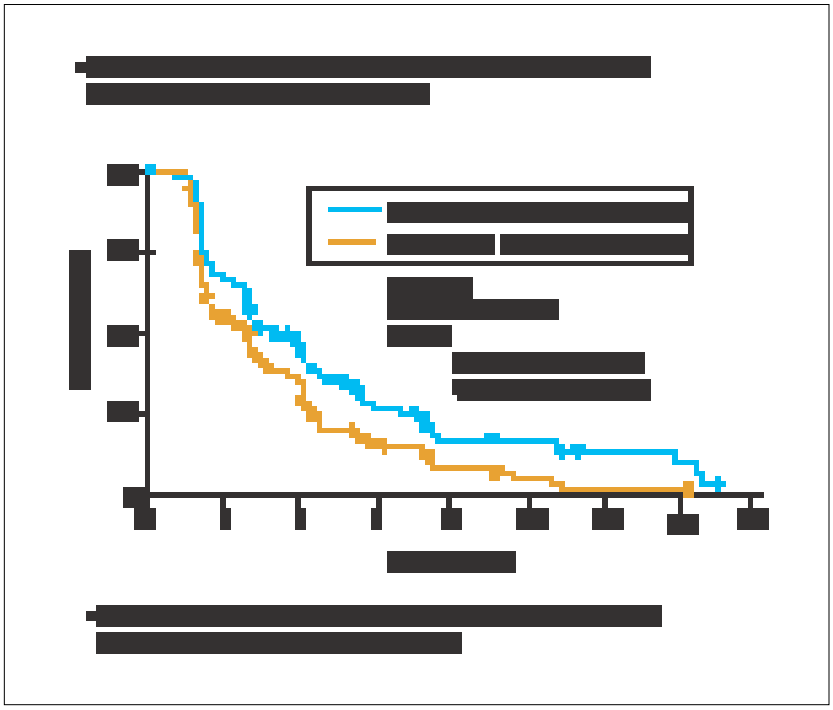

Figure 5. Baseline VEGF as a prognostic indicatorin RCC.

Data from Bukowski et al[57]; Jacobsen et al *J Urol*. 2000;163:343-347.

CI=confidence interval; HR=hazard ration; PFS=progression-free survival; RCC=renal cell carcinoma; VEGF=vascular endothelial growth factor.

discussed above.[94] Production of VEGF can be decreased through inhibition of mTOR, an upstream regulator of HIF-1α, and small-molecule TKIs inhibit VEGFR. A third mechanism of therapeutic intervention of this pathway is targeting the VEGF molecule itself.[95] Three of these VEGF-targeting agents have been extensively tested in the clinical setting: bevacizumab, VEGF Trap, and IMC-1121B.

Clinical Results With Bevacizumab

Bevacizumab is a monoclonal antibody that binds to circulating VEGF-A molecules, thereby neutralizing their ability to interact with and activate VEGFR.[96] Second-line bevacizumab was shown to be safe and efficacious in a proof-of-principle double-blind phase II trial of 116 patients.[97] Patients who had received prior therapy with IL-2 were randomized to receive either placebo, low-dose bevacizumab (3 mg/kg), or high-dose bevacizumab (10 mg/kg) every 2 weeks. Those individuals receiving high-dose bevacizumab experienced a superior mean PFS rate compared to placebo (4.8 vs 2.5 months, respectively; $P<.001$), and higher rates of OR (10% vs 0%, respectively). Although the clinical response rates were quite low, the majority of patients receiving high-dose bevacizumab showed some evidence of tumor regression compared to the low-dose or placebo groups.[98]

The success of bevacizumab in this and subsequent trials prompted its evaluation in combination with other agents. One institutional single-arm study combined bevacizumab with erlotinib in 63 patients with mRCC.[99,100] CRs were observed in 3% of patients, while 22% had a PR and 61% had SD. This relatively high OR rate resulted in 1- and 2-year PFS rates of 45% and 24%, respectively. Likewise, the median time-to-progression and median OS were 11.1 and 22.8 months, respectively. These results were surprising in light of the fact that EGFR inhibition had previously been shown to have very little effect in mRCC.[101] To determine if these results were due to the combination of bevacizumab and erlotinib or to bevacizumab alone, a phase II trial was initiated.[102] In this study, 104 patients with mRCC were randomized to receive either bevacizumab alone or in combination with erlotinib, both as first-line therapy. After a median follow-up of 9.8 months, the median PFS was found to be similar in both the single-agent and combination treatment arms (8.5 and 9.9 months, respectively), corresponding to a nonsignificant HR of 0.86 (95% CI, 0.5–1.49). There was also no difference in OR rates (13% vs 14%, respectively). Although the addition of erlotinib to bevacizumab was well tolerated, it offered no additional benefit over single-agent bevacizumab.

Two phase III studies have investigated the combination of IFNα with bevacizumab. Preliminary results of the CALGB study are expected to be reported in the near future.[103] The AVOREN trial was a large phase III study that evaluated the combination of bevacizumab with IFNα in 649 mRCC patients.[104] All enrolled patients had undergone a nephrectomy. Individuals were randomized

to receive either this combination therapy or IFNα alone as first-line therapy until disease progression. Median PFS was significantly longer in the combination arm versus the IFNα-only arm (10.2 vs 5.4 months, respectively; HR, 0.63; 95% CI, 0.52–0.75; *P*=.0001). This improvement in PFS was observed in both the low- and intermediate-risk groups, but no difference was noted in the high-risk group of patients. Additionally, the combination therapy resulted in a significantly superior rate of OR compared with IFNα only (31% vs 13%; *P*<.0001). The combination was well tolerated, and the most frequently reported grade 3 or 4 adverse events were fatigue (12%) and asthenia (10%). Additionally, hemorrhage (3.3%), venous thromboembolism (1.8%), and gastrointestinal perforation (1.5%) were reported more frequently in the combination group, due to the antiangiogenic properties of bevacizumab. Yet to be tested is whether IFNα is a necessary component for the benefit noted in the bevacizumab combination arm, and future studies will answer this question.

Other combinations with bevacizumab have been evaluated in phase I clinical trials. Bevacizumab in combination with temsirolimus produced an OR rate of 67% in a small patient population (N=12).[105] Combination with either sorafenib or sunitinib resulted in OR rates of 46% and 37%, respectively, in two separate trials.[106,107] These preliminary studies have led to the development of phase II studies to further evaluate the safety and efficacy of these combinations.

"Trapping" VEGF

Like bevacizumab, VEGF Trap binds to extracellular VEGF, inhibiting it from interacting with VEGFR. However, VEGF Trap is unlike bevacizumab in that it is an engineered version of the VEGFR, composed of portions of both VEGFR-1 and -2 fused to the Fc portion of a human IgG antibody.[108] It is also able to interact with VEGF with a much higher affinity than bevacizumab. To date, VEGF Trap has only been tested in a limited fashion in RCC, predominantly through phase I studies along with other advanced solid malignancies. One such phase I pharmacokinetic study included 9 patients with RCC.[109] The adverse events reported in this trial were similar to those previously reported for bevacizumab. E4805 is an ongoing randomized phase II trial designed to determine the effect of VEGF Trap at two different doses in patients with previously treated mRCC.

IMC-1121B

IMC-1121B is a fully human monoclonal antibody directed against the extracellular portion of VEGFR-2. Binding to the receptor prevents VEGF binding, thereby limiting VEGF-stimulated activation. IMC-1121B is currently in early-phase clinical in RCC. An open-label phase II study is currently underway in 36 patients, with the primary objective of OR rate.

Summary—2008 Treatment Algorithm for RCC

To most effectively incorporate the novel therapeutic agents discussed here into current treatment regimens, patients should be stratified into prognostic risk groups. The need for such stratification became especially apparent after it was realized that these patient subgroups responded differently in the first-line setting in various phase III trials. For initial therapy of RCC, sunitinib is clearly the predominant agent with which low- and intermediate-risk patients should be treated. High-dose IL-2 is also an option for these patients, and bevacizumab may be considered. For poor-risk patients temsirolimus offers the most benefit as a first-line agent. As second-line therapy, sorafenib is the ideal drug for patients who have received prior cytokine treatment. For those patients who have received prior VEGF pathway inhibitors, no choice has been clearly established, and phase III trials are in progress.

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Notes

Translating Biology to Clinical Practice: Evolving Strategies for the Treatment of Renal Cell Carcinoma

CME Post-Test: *Circle the correct answer for each question below.*

1. Which of the following factors is NOT considered part of the Memorial Sloan-Kettering Cancer Center nomogram for RCC risk assessment?

   a. Low hemoglobin
   b. Absence of prior nephrectomy
   c. High corrected potassium
   d. Low Karnofsky performance status

2. In a study presented by Dr. Wood of over 1600 patients at the Mayo Clinic, patients with either N0 or Nx clear-cell RCC had a 1-year survival rate of _____, compared with only _____ for patients with either N1 or N2 disease.

   a. 95.5%; 52.5%
   b. 52.5%; 95.5%
   c. 83.2%; 25.4%
   d. 64.5%; 25.4%

3. For patients with localized RCC, a _____ histology was shown to predictive of better prognosis, as these patients had a median 5-year cancer-specific survival of 88%.

   a. clear-cell
   b. chromophobe
   c. papillary
   d. benign oncocytoma

4. For patients with metastatic RCC, a _____ histology was associated with a negative prognosis, and patients had a median 5-year cancer-specific survival of 0%.

   a. clear-cell
   b. chromophobe
   c. papillary
   d. benign oncocytoma

5. In a phase III study presented by Dr. Bukowski, sunitinib was shown to more than double PFS of treatment-naive mRCC patients over IFNα treatment, resulting in a median PFS of _____.

   a. 5 months
   b. 8 months
   c. 9 months
   d. 11 months

6. The TARGET trial found that _____ was superior to placebo in treatment-refractory patients with advanced disease.

   a. IFNα
   b. sunitinib
   c. sorafenib
   d. pazopanib

7. A phase III trial discussed by Dr. Quinn showed that frontline therapy with single-agent temsirolimus resulted in a median PFS of _____, which was significantly superior to the median PFS produced by IFNα treatment.

   a. 1.9 months
   b. 3.8 months
   c. 4.5 months
   d. 4.9 months

8. True or False? In a post hoc analysis of the phase III temsirolimus trail, patients with MSK poor risk status had a better OS than those receiving IFN?

   a. True
   b. False

9. When the function of the _____ protein is disrupted, the HIF-1α protein is stabilized and able to promote transcription of downstream target genes, including VEGF.

   a. Raf
   b. Ras
   c. VEGFR
   d. VHL

10. A phase II trial discussed by Dr. Hutson showed that the addition of _____ to bevacizumab offered no additional benefit over bevacizumab therapy alone, with a median PFS of 9.9 months and 8.5 months, respectively.

    a. temsirolimus
    b. erlotinib
    c. sorafenib
    d. sunitinib

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