Clinical Medicine Reviews in Oncology

REVIEW

Bevacizumab in Combination with Interferon Alpha in Metastatic Renal Cell Carcinoma: The Emerging Evidence of Its Therapeutic Value

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Abstract: Cytokine therapy provides inadequate disease control and poor survival outcomes for patients with metastatic renal cell carcinoma (mRCC). Refined understanding of RCC biology identified molecular targets for the application of novel inhibitors. The monoclonal anti-VEGF antibody, bevacizumab, demonstrated efficacy and safety in phase II testing in patients with cytokine-refractory advanced RCC. The combination of bevacizumab and interferon significantly improved response rate and progression-free survival in two randomized phase III trials (AVOREN and CALGB 90206). The toxicity profile of the combination relates largely to that known to be associated with interferon. The contribution of Interferon to the combination's overall efficacy has been questioned. Because FDA approval of bevacizumab plus interferon did not specify the line of therapy, the place of the combination among other therapies (including tyrosine kinase and mTOR inhibitors) is the subject of debate. Trials of combinations of bevacizumab and other targeted agents (eg, erlotinib, temsirolimus) have produced unacceptable toxicity. There are ongoing trials designed to investigate the efficacy of bevacizumab monotherapy and bevacizumab in combination with attenuated dose of interferon or in combination with mechanistically different targeted agents.

Keywords: bevacizumab, interferon, combination, angiogenesis, VEGF, renal cell carcinoma, safety, efficacy, survival

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Introduction

In the year 2010, 58,240 new cases of renal cell carcinoma (RCC) and 13,040 related deaths were expected in the United States alone.[1] Worldwide, the disease was expected to affect 287,421 people and cause 122,303 deaths in the same year.[2] Forty percent of patients who present with early-stage disease ultimately develop metastatic recurrence.[3] In the era when interferon (IFN) was the standard of care for metastatic RCC (mRCC), the prognosis was generally poor with 5-year survival rate close to 20% even in the best prognostic group.[4,5] RCC has historically been insensitive to cytotoxic chemotherapy and traditional radiotherapy. Although the former continues to be of limited utility in advanced disease, novel radiosurgical techniques are increasingly being employed for local control.[6,7] However, an improved understanding of the biology underlying RCC tumorigenesis has driven the development of several molecularly targeted agents. While many clinical trials in mRCC have only demonstrated prolongation of progression-free survival, in clinical practice, sequential application of VEGF pathway inhibitors and mTOR inhibitors has clearly improved overall survival. Specifically, novel agents that inhibit the vascular endothelial growth factor (VEGF) pathway (eg, bevacizumab, sunitinib, sorafenib, and pazopanib) and the mTOR pathway (eg, temsirolimus and everolimus) have generated meaningful clinical activity against RCC. These therapeutic advances have shattered the conception of RCC as a disease refractory to systemic therapy, altered the natural history of the disease, and transformed the prognostic outlook for patients.

Soon after bevacizumab became the first VEGF targeted agent to demonstrate efficacy as monotherapy in mRCC, investigators explored the value of combining it with the *de facto* standard of care, IFN.[8] This work led to two pivotal randomized phase III trials, AVOREN and CALGB 90206, and resulted in the regulatory approval of bevacizumab in combination with IFN for patients with mRCC. Beyond establishing the safety and efficacy of bevacizumab plus IFN, these two trials generated observations that called into question the value of IFN in the context of the combination. This review will address the clinical experience with IFN prior to the era of VEGF targeted therapy; highlight the biological rationale of bevacizumab development; and discuss the current role of bevacizumab plus IFN in the management of advanced RCC. The review will also outline ongoing clinical trials of novel bevacizumab-based combinations which should help define its role in the future therapy of mRCC.

Immunogenic Biology of RCC

The immunogenic nature of RCC was elucidated from observations of metastatic regression following surgical resection of primary tumor. Efforts to boost immune response against RCC tumors focused on the utility of IFN and high-dose interleukin-2 (HDIL-2), which, to date, have produced the most consistent antitumor activity. Two cytokines, IFN and IL-2, emerged as the critical mediators of immunogenic recognition, suppression and, even, eradication of RCC. The mechanism by which IFN and IL-2 suppress tumor cell growth is not well-known. They are thought to regulate cellular differentiation and induce apoptosis by interfering with signal transduction pathways involving signal transducer and activator of transcription (STAT), tissue transglutaminase (TTG), and possibly others. IFN appears to exert antiangiogenic properties and, along with IL-2, it stimulates cytotoxic lymphocyte and natural killer cell recognition and eradication of tumor cells.[9–11] IFN had long been the *"de facto"* standard of care and, therefore, served as the control arm of randomized clinical trials aiming to establish the efficacy and safety of novel agents.

Single Agent Interferon in mRCC

Historically, IFN was the most commonly applied therapy for patients with mRCC because it was easier to administer than interleukin-2 based regimens and had been shown to offer a small survival benefit in randomized clinical trials.[12–14] The toxicity profile of single agent IFN was predictable and included flu-like symptoms (myalgias, arthralgias, anorexia, fevers, and chills), taste changes, pancytopenia, transaminitis. These symptoms were more prominent in older patients but tended to abate over time. In several trials, IFN produced objective response rates as high as 10%–15%, mostly partial, with median time to response of 4 months and a response duration that rarely extended beyond one year. Evidence supporting the survival advantage of interferon monotherapy

was bolstered by a Cochrane meta-analysis involving 644 patients from four studies. Treatment with IFN was clearly superior to controls (including hormones and chemotherapy), with odds ratio for death at one year 0.56 (95% CI 0.4–0.77) and overall hazard ratio for death 0.74 (95% CI 0.63–0.88). The median survival time was 12 months.[15] Recognition of IFN's limited efficacy against RCC prompted research into novel IFN-based combination regimens to improve response rate and survival outcomes. Investigators combined IFN with cytotoxic chemotherapy, antiproliferative agents, and hormones but failed to demonstrate significant advantage over IFN alone. However, the development and validation of molecularly targeted therapies set the stage for clinical investigation of more promising IFN-based combinations.

Vascular Endothelial Growth Factor and Angiogenesis

The growth of clear-cell RCC relies heavily on its ability to recruit new blood vessel formation through the process of angiogenesis. The vast majority of RCC tumors are biologically addicted to the over expression of VEGF whose levels correlate with RCC tumor stage and prognosis.[16,17] In normal tissue, the protein von Hippel Lindau (pVHL) modulates the activity of the transcription factor, hypoxia-inducible factor-alpha (HIF-α), the central regulator of cellular response to hypoxia. Under normoxic conditions, pVHL targets the hydroxylated form of HIF-α for ubiquitin-mediated proteasomal degradation. Hypoxic stress, on the other hand, elicits expression of a de-hydroxylated form of HIF-α, which eludes substrate binding by VHL, translocates to the nucleus, and induces the expression of a number of growth and angiogenic factors, including the vascular endothelial growth factor (VEGF). An event that defines the vast majority of sporadic clear cell RCC, biallelic inactivation of the VHL gene, results in expression a defective pVHL and accumulation of HIF-α. The latter unleashes vigorous expression and elaboration of VEGF by tumor cells.[18,19] VEGF stimulates endothelial cell proliferation and new blood vessel formation and fuels tumor growth and progression[19] (Fig. 1). The VEGF receptor and the specific signaling cascade it activates have served as logical targets of new anti-RCC agents. These included VEGF neutralizing antibodies (eg, bevacizumab) tyrosine kinase inhibitors (eg, sunitinib) and mTOR antagonists (eg, everolimus), all of which abrogated the angiogenic sequence at different levels.

Efficacy and Safety of Bevacizumab in mRCC: Phase II Results

Bevacizumab is a VEGF-targeted monoclonal antibody with clinical activity against mRCC, both as monotherapy and in combination with other agents. In a landmark phase II study, Yang and colleagues established the therapeutic role of VEGF inhibition in mRCC. The placebo-controlled and randomized study demonstrated that bevacizumab was both safe and efficacious in patients with mRCC who had failed immunotherapy. One-hundred and sixteen patients were randomized to one of three arms—placebo, bevacizumab 3 mg/kg q2w, and bevacizumab 10 mg/kg. An interim analysis revealed that bevacizumab at 10 mg/kg significantly prolonged time to progression (TTP) of 2.3 months compared to placebo (4.8 vs. 2.5 months, $P < 0.001$). At the lower dose of 3 mg/kg, therapy with bevacizumab produced a modest improvement in TTP, which was not statistically significant (3 vs. 2.5 months; $P < 0.053$) (Fig. 2). At 10 mg/kg, bevacizumab induced an overall response rate of 10.3%, all of which were partial, while no responses were observed in either the low-dose arm or placebo. The antibody was well-tolerated with no grade 4 or 5 toxicities. Grade 3 toxicities were largely limited to asymptomatic and reversible hypertension and proteinuria (Table 1).[8]

The safety and efficacy of bevacizumab was further illustrated in another placebo-controlled, randomized, phase II trial that compared bevacizumab 10 mg/kg plus erlotinib 150 mg to bevacizumab alone. In this study, which demonstrated no significant difference in the PFS or ORR between the two arms, the bevacizumab monotherapy group demonstrated a PFS of 9.9 months and overall response rate of 14% (Fig. 2). Both arms also demonstrated similar rates of hypertension and proteinuria but diarrhea and rash were more common in the bevacizumab plus erlotinib arm. One death, due to ischemic bowel and GI perforation, occurred in the combination arm while none occurred in the bevacizumab arm. Three patients in

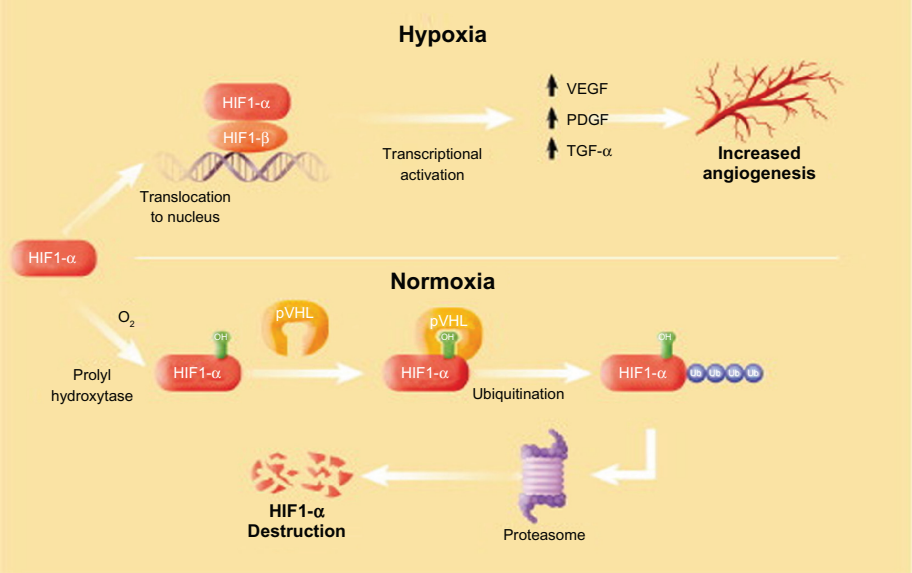

Figure 1.
Reprinted from *Cancer Treatment Reviews*, 36(3), McDermott DF, George DJ, Bevacizumab as a treatment option in advanced renal cell carcinoma: an analysis and interpretation of clinical trial data, 216–23, copyright 2010, with permission from Elsevier.
Abbreviations: HIF-1α, hypoxia-inducible factor alpha; PDGF, platelet-derived growth factor; TGF-α, transforming growth factor alpha; pVHL, von Hippel–Lindau tumor suppressor protein; VEGF, vascular endothelial growth factor.

the bevacizumab arm discontinued therapy due to adverse events, which included bowel fistula, acute renal failure, and hypertension. The rate of grade 3 adverse events in the bevacizumab arm, in which no grade 4 toxicities were seen, was 59% and included hypertension (26%), hemorrhage (4%), proteinuria (6%), heart failure (2%) and acute renal failure (4%).[20] The outcome of this trial offered a cautionary tale about the limiting toxicities that can result from simultaneous blockade of multiple signaling pathways.

Combination of Bevacizumab and Interferon

AVOREN

Inspired by the activity of bevacizumab in phase II testing, the AVOREN and CALGB 90206 trials were launched to investigate the clinical benefit of combined antiangiogenic therapy with IFN. The two randomized, phase III, multicenter clinical trials assessed the relative benefit of adding bevacizumab to interferon in the first line treatment of mRCC. In both trials, patients were randomized to bevacizumab plus IFN versus IFN alone. Unlike CALGB, AVOREN (N = 649) was placebo-controlled, double-blinded, and mandated prior nephrectomy, either total or partial nephrectomy with negative surgical margins. The primary endpoint of this trial was overall survival while PFS, ORR, and safety were secondary. While the study was underway, many active second-line therapies (eg, TKIs) became available and preliminary PFS data from CALGB trial favoring bevacizumab approached fruition. Concerns about confounding of overall survival data analysis by cross-over to active second-line therapies or bevacizumab following disease progression on the control arm prompted the authors to unblind the trial and report the results in 2007 at the time of a preplanned final PFS analysis. Median overall survival had not been reached in the bevacizumab plus interferon arm. Compared to interferon alone, the combination arm demonstrated significantly better median PFS (10.4 vs. 5.5 months, $P = 0.0001$), ORR (31% vs. 13%; $P = 0.0001$), and median time to progression (10.2 vs. 5.5 months; $P = 0.0001$) (Fig. 3).[21] The OS survival data analysis was subsequently published in 2010 and demonstrated no significant survival difference between two arms (23.3 vs. 21.3 months, $P = 0.1291$).[22]

Interestingly, reduction of the dose of IFN to 6 or 3 MIU, which was driven by toxicity in 40% of patients in the treatment arm and 30% in the control arm, did not appear to compromise PFS benefit. The progression-free survival rate for patients in the bevacizumab

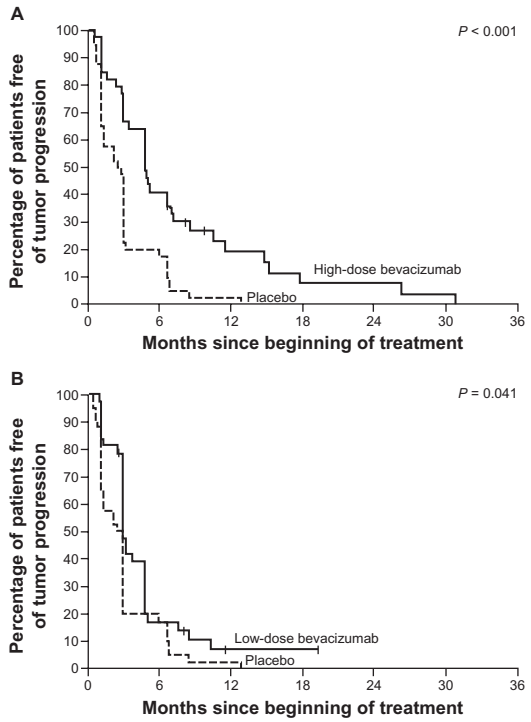

Figure 2. Kaplan-Meier analysis of survival free of tumor progression for patients receiving high-dose bevacizumab (**Panel A**) or low-dose bevacizumab (**Panel B**), as compared with placebo.
Reprinted from *New England Journal of Medicine*, 349(5), Yang JC et al, A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer, 427–34, copyright 2003, with permission.

group at 1 year was 43% compared with 52% in the dose-reduced patients. A subgroup analysis further demonstrated that PFS benefit was independent of sex, age, performance status, baseline VEGF level, presence or absence of pulmonary metastases, or the number of metastatic sites. In the same analysis, only favorable and intermediate-risk MSKCC groups retained significant PFS benefit while the poor-risk group did not. The latter group, it must be point out, comprised only 8% of the patient population. Unstratified subgroup analysis of the OS revealed the treatment effect was maintained across a variety of baseline disease characteristics with a subgroup HR similar to that of the overall population. Subgroup analysis of overall survival stratified by MSKCC risk group revealed death risk reduction that was similar across all subgroups in favor the bevacizumab plus IFN arm (Fig. 4).[21]

Serious adverse events were reported in 30% of patients who received combination therapy compared to 16% of those who received IFN alone. In both groups, the most commonly reported toxicities of grade 3 or higher were those related to IFN (eg, fatigue, asthenia, and neutropenia). The incidence of these symptoms was 10% higher in the combination arm. Bevacizumab-related toxicities, such as proteinuria, bleeding and hypertension, were seen only in the combination group. Only 2% and 5% of those with hypertension and proteinuria discontinued therapy due to these particular toxicities. GI perforation and thromboembolic events occurred in 1% and 3%, respectively, of patients in the bevacizumab group. The death rate due to adverse events was identical in both groups at 2%. Only 3 deaths (<1%), 2 related to bleeding and 1 related

Table 1. Toxic effects of any grade that occurred in at least 10% of patients receiving either dose of antibody and were more frequent than placebo group.

Effect	High-dose bevacizumab (N = 39)	Low-dose bevacizumab (N = 37)	Placebo (N = 40)
	Number		
Epistaxis	8†	5	1
Hypertension	14† (8†)	1	2
Fever without infection	4	1	0
Malaise	13	6	6
Hematuria	5†	1	0
Hyponatremia	3	4†	0
Proteinuria (≥1+ or ≥150 mg/24 hr)	25† (3)	15 (2)	15
Elevated alanine aminotransferase	4	2	0
Chest pain	2 (2)	0	0

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Notes: The number of patients with grade 3 toxic effects is shown in parentheses. Every bevacizumab-associated grade 3 toxic effect occurring in more than one patient is shown. †Unadjusted $P \leq 0.05$ for the comparison with placebo (by chi-square test, or by Fisher's exact test if the expected frequency was less than 5).

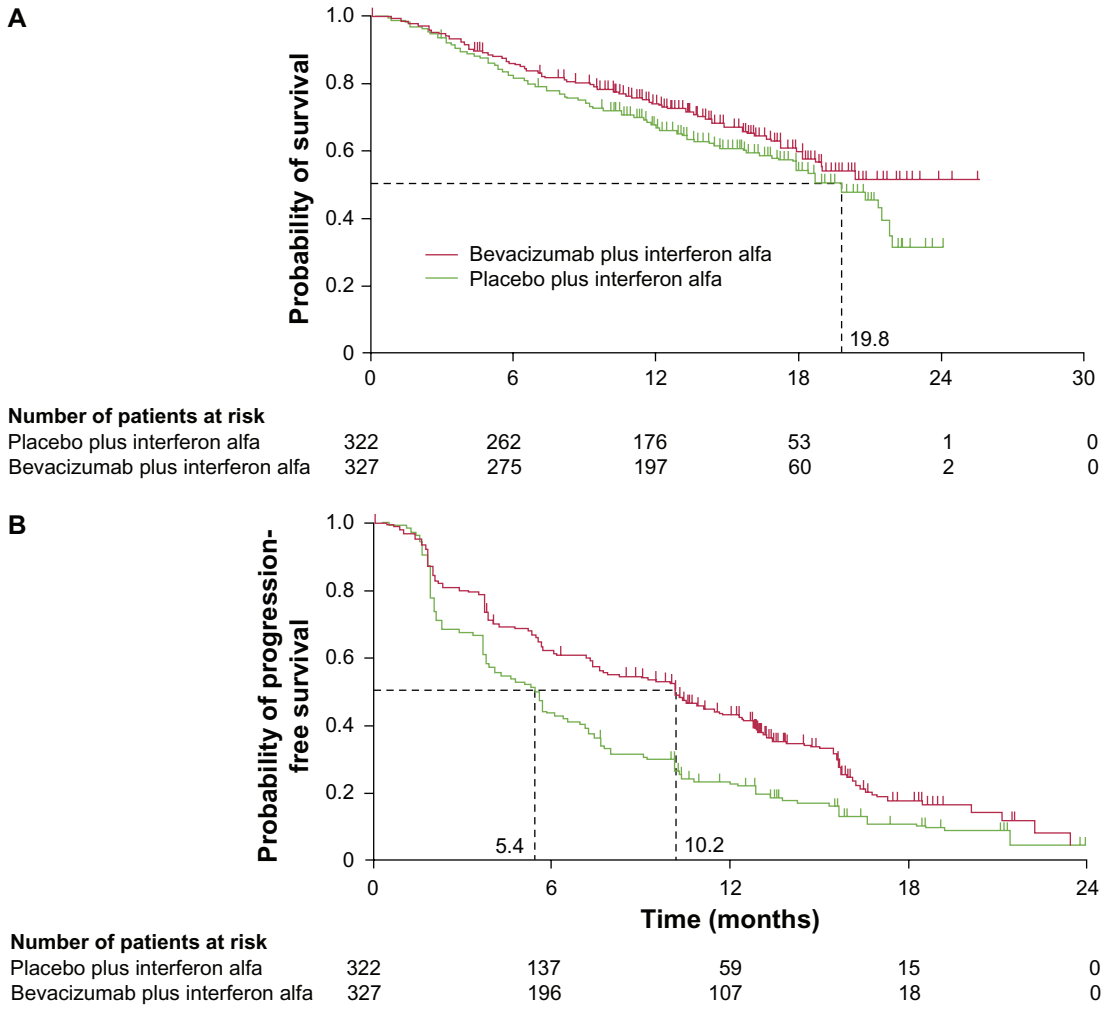

Figure 3. Kaplan-Meier estimates of (**A**) overall survival and (**B**) progression-free survival (PFS). Interim analysis of overall survival based on 251 of 450 scheduled events. Median overall survival had not been reached in the bevacizumab plus interferon alfa group. Final analysis of PFS based on 505 progression events.
Reprinted from The *Lancet*, 370, Escudier B, et al, Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial, 2103–11, copyright 2007, with permission from Elsevier.

to GI perforation, were deemed possibly related to bevacizumab.[21]

CALGB 90206

Further confirmation of the superiority of bevacizumab plus IFN to IFN alone came from the CALGB 90206 trial. Unlike AVOREN, CALGB 90206 was an open-labeled study and did not require prior nephrectomy. The eligibility criteria, statistical design and data analysis were similar to those of AVOREN's. In CALGB 90206, OS was the primary endpoint, while PFS and objective response rate (ORR) were secondary. Relative to IFN alone, therapy with bevacizumab plus IFN significantly improved ORR (25.5% vs. 13.1%, $P < 0.0001$) and median PFS (8.4 vs. 4.9 months, $P < 0.0001$). Overall survival, on the other hand, was similar in both arms—18.3 months in the combination arm and 17.4 months in the IFN-only arm ($P = 0.097$). Subgroup analysis demonstrated no significant difference in median overall survival based on prior nephrectomy status, MSKCC risk group, and presence of liver metastases, age, or gender. Stratification of patients by MSKCC risk groups demonstrated that, compared to IFN alone, combination therapy achieved a median OS of 32.5 months (versus 33.5 m, $P = 0.524$) in the favorable risk group, 17.7 months (versus 16.1 months, $P = 0.174$) in intermediate risk group and 6.6 months versus 5.7 months in the poor-risk group ($P = 0.25$). Similarly, stratification by MSKCC risk group demonstrated the median PFS favored the treatment arm across

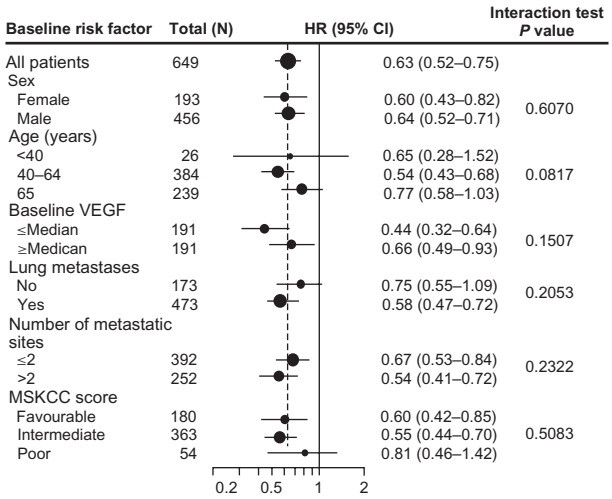

Figure 4. Subgroup analysis of progression-free survival in the AVOREN trial.
Reprinted from The *Lancet*, 370, Escudier B, et al, Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial, 2103-11, copyright 2007, with permission from Elsevier.

all three groups—11.1 versus 5.7 m in the favorable risk group (26% of all patients); 8.4 versus 5.3 months in the intermediate risk group (64%); and 3.3 versus 2.6 months in the poor risk group (10%). Interestingly, retrospective analysis of the trial demonstrated that development of 2 hypertension of at least grade 2 on the combination arm was associated with significantly better PFS and OS. On multivariate analysis, development of HTN at 2 months was an independent predictor of OS. (HR 0.622, $P = 0.046$).[23]

Patients in the combination arm had a significantly higher incidence of grade 3–5 toxicities (80% vs. 60%, $P < 0.001$) including hypertension (11% vs. 0%), and proteinuria (15% vs. <1%), anorexia (17% vs. 8%), and fatigue (37% vs. 30%). The incidence of grade 4 hematologic toxicity, febrile neutropenia, requirements for blood transfusions, and treatment related deaths (4 in the IFN-only arm and 3 in the bevacizumab arm) was similar As in AVOREN, however, overall, the most commonly reported grade 3–5 toxicities were IFN-related and included fatigue and neutropenia. IFN dose reduction to 6 MU and 3 MU were necessary in 46% and 18%, respectively. The authors did not elaborate on whether IFN dose reduction was associated with significant change in PFS.[23]

As in the AVOREN trial, the authors of the CALGB trial speculated that the absence of an overall survival benefit could be due to second-line therapies. In fact, sixty-two percent of patients on IFN monotherapy and 54% of patients on the bevacizumab plus IFN received subsequent systemic therapy following disease progression. The majority received VEGF-receptor tyrosine kinase inhibitors (sunitinib and sorafenib). To control for potential confounding of survival data, the authors performed post-hoc analysis of the impact of second-line therapy on overall survival according to whether or not second-line therapy was received. Those who did following disease progression in the combination arm demonstrated a median OS of 31.4 months compared to 26.8 months ($P = 0.079$) in the IFN monotherapy arm. Among patients who did not receive second-line therapy, the median OS was 13.1 months in the combination arm versus 9.1 months ($P = 0.059$) in the IFN monotherapy arm.[23] The AVOREN AND CALGB trials represent important milestones in the search for active therapeutics for advanced RCC. However, IFN's significant toxicity has in reality tempered enthusiasm for the routine use of the combination in clinical practice. The efficacies of bevacizumab monotherapy or in combination with attenuated dose of IFN are the subject of further investigation (see below).[24,25]

Integrating Bevacizumab Plus Interferon into Treatment Guidelines

Algorithm of mRCC therapy

The results of the AVOREN trial led both the EMEA and the FDA to approve the use of the combination of bevacizumab and IFN for the treatment of mRCC. Unlike EMEA whose approval favored utilization in the first-line setting, the FDA made no specific recommendation regarding the line of therapy. One potential algorithm for the selection of initial treatment of mRCC reflects recommendations of the NCCN and those of experts in the field and is outlined in Figures 5 and 6. Patients who are suitable candidates should be offered HDIL-2 whenever possible. Patients in the MSKCC good or intermediate risk groups may be offered bevacizumab plus IFN, sunitinib, pazopanib, or, alternatively, sorafenib. On the other hand, poor-risk patients should receive temsirolimus, or, alternatively, sunitinib or pazopanib. Patients with non-clear cell histology may be offered temsirolimus or, alternatively, sunitinib.[26–31]

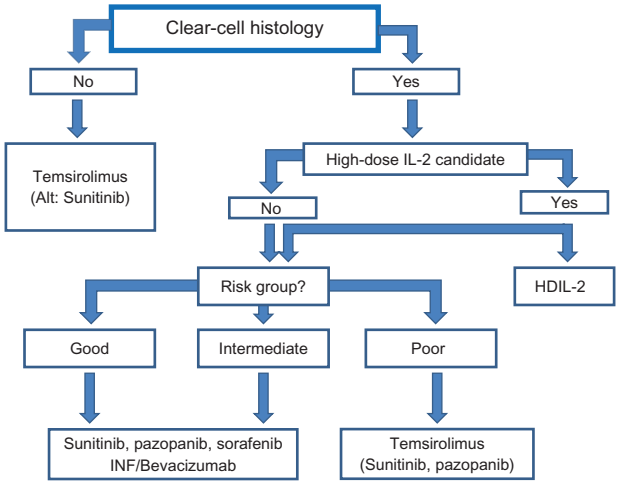

Figure 5. Proposed algorithm for first-line treatment of patients with metastatic renal cell carcinoma.[28]
Abbreviations: Alt, alternate therapy; IFN, interferon; HDIL-2, high-dose interleukin 2.

Selecting the optimal choice of first-line therapy must involve careful analysis of toxicity profile, patient co-morbidities, and relative impact on quality of life.[32] Unlike TKIs, bevacizumab produces little in the way of off target toxicities.[33] TKIs can precipitate painful hand-foot syndrome with dramatic quality of life implications for patients with limited mobility or poor performance status. TKI use in patients with cardiac risk factors must entail careful monitoring for signs of congestive heart failure, which occurs at a rate as high as 8%.[34] On the other hand, history of thromboembolic disease, severe diverticulosis, or poorly controlled hypertension should prompt reconsideration of the safe use of bevacizumab.[35,36]

First line		Second line
HDIL-2	→	Sunitinib, pazopanib, sorafenib or bevacizumab/INF
Sunitinib Pazopanib	→	Everolimus (Alt: Sorafenib or bevacizumab/INF)
Bev/INF	→	Sunitinib, pazopanib or sorafenib
Sorafenib	→	Everolimus (Alt: Sunitinib, pazopanib or bevacizumab/INF)
Temsirolimus	→	Clinical trials

Figure 6. Proposed algorithm for second-line treatment of patients with metastatic renal cell carcinoma.[28]
Abbreviations: Alt, alternate therapy; IFN, interferon; HDIL-2, high-dose interleukin 2.

Is full-dose interferon necessary?

As noted earlier, in the AVOREN trial, IFN dose reduction, which was necessary in 30%–40% of patients, did not compromise efficacy and significantly improved patient tolerability. The rates of IFN-specific adverse effects (including flu-like symptoms, fatigue and asthenia) were reduced considerably. A retrospective analysis of data from the AVOREN trial confirmed that INF dose reduction to 3 or 6 MIU/week retained clinical benefit and considerably reduced toxicity.[37] At least in theory, this observation carries the implication that it may be feasible to both minimize IFN-related toxicities *and* maintain clinical efficacy. Translating this implication to clinical practice, however, mandates prospective validation, which is the subject of a phase II clinical trial currently underway in Europe. This trial aims to assess the safety and efficacy of bevacizumab plus lower-dose INF (3 MIU tiw).[24] Furthermore, the same observation prompts the intriguing question of whether INF added any therapeutic value and, if so, how much. The relative contribution of INF can be assessed only in the setting of a randomized trial that compares the efficacy of bevacizumab plus INF to that of bevacizumab alone.

Sequencing Bevacizumab Following Failure Tyrosine Kinase Inhibitors

Sequencing of targeted therapies has been the focus of several prospective and retrospective studies. The safety and efficacy of TKIs following bevacizumab has been demonstrated in several prospective and retrospective studies. The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) study demonstrated that, in bevacizumab-refractory patients (n = 197), sorafenib achieved a PR and SD rates of 3% and 78%, respectively.[38] In another prospective trial, the use of sunitinib following progression on bevacizumab generated an ORR of 23% and median PFS of 30.4 weeks.[39] Unfortunately, there is a paucity of studies published to date addressing the safety and efficacy of bevacizumab in TKI-refractory patients. A recent phase II study compared the efficacy of the combination of bevacizumab plus everolimus in TKI-refractory versus untreated patients reported PR and SD rates of 17% and 59%, respectively. The authors concluded that the bevacizumab-containing combination

retained activity and safety despite prior TKI exposure.[40] However, more studies are needed before such a conclusion can be definitively reached.

Combining Bevacizumab and Tyrosine Kinase Inhibitors

Regimens combining bevacizumab with TKIs have been the subject of several trials, which aimed to examine the therapeutic implications of VEGF pathway inhibition at various points (vertical blockade). In many, however, safety emerged as a formidable concern. For example, the combination of bevacizumab plus sunitinib (25–50 mg daily) produced notable efficacy in a phase I trial. However, it was poorly tolerated by a considerable fraction of patients who developed grade 3 and 4 toxicities. The latter included two cases microangiopathic hemolysis, which prompted dose reduction or study discontinuation.[41] Similarly, another trial of combination targeted therapy with sorafenib and bevacizumab showed that the improvement in antitumor efficacy was accompanied by enhanced toxicity.[42]

Combining Bevacizumab and mTOR Inhibitors

Combining VEGF blockade with bevacizumab and mTOR inhibition has generated encouraging preliminary results. A single-arm phase II trial of bevacizumab plus everolimus in clear-cell mRCC demonstrated good activity and tolerable toxicity. The patient population included both treatment-naïve patients and patients previously treated with sunitinib or sorafenib. The median progression-free survival in previously untreated and previously treated patients was 9.1 and 7.1 months, respectively. Overall response rates were similar in both groups (30% and 23%, respectively). Although most patients tolerated the combination, the incidence of grade 3–4 proteinuria was 25% and led to treatment discontinuation in 6 patients. The authors concluded that the combination of bevacizumab and everolimus was active and well tolerated in the treatment of mRCC following sunitinib and sorafenib failure.[43]

The randomized phase 2 trial (TORAVA) assigned treatment-naïve clear-cell mRCC patients to one of three arms: 1) combination of bevacizumab plus temsirolimus; 2) 42 patients received single agent sunitinib; or, 3) bevacizumab plus IFN. The percentage of patients who were progression-free at week 48 was 43% on the bevacizumab-temsirolimus arm, 48% for single agent sunitinib arm, and 66% on bevacizumab-interferon arm. Whereas response rates were similar across the three arms, the bevacizumab-temsirolimus arm was associated with high incidence (36%) of grade 3–4 toxicities and 2 toxic deaths. The small sample size of this trial notwithstanding, the results seem to call into question the wisdom of pursuing phase III testing of this regimen.[44]

The phase II BeST trial randomized patients with predominantly clear cell mRCC and no prior antiangiogenic treatment to one of four arms—bevacizumab monotherapy, bevacizumab plus temsirolimus, bevacizumab plus sorafenib, or temsirolimus plus sorafenib. While this trial has completed accrual, data collection is expected to conclude in 2012. The findings from this trial will provide further insight into the safety and efficacy of the bevacizumab-temsirolimus combination. They will also shed light on the activity of bevacizumab monotherapy (without IFN) in mRCC.[45] The efficacy of combining of bevacizumab and IFN with chemotherapy is the subject of ongoing investigation. A phase II single arm trial of bevacizumab, INF, and vinblastine is in the accrual phase.[46] In addition, a randomized phase III study of the combination of bevacizumab plus temsirolimus compared with bevacizumab with IFN as front-line therapy for patients with advanced RCC is underway.[45]

Conclusion

Molecularly targeted therapy has emerged as a preferred treatment approach for patients with mRCC. The past decade has witnessed rapid development of drugs that inhibit the VEGF and mTOR pathways at various points. Bevacizumab, both as monotherapy and in combination with IFN, demonstrated activity against advanced RCC. The combination offers superior progression-free survival compared to interferon alone and is approved as first-line treatment of patients with mRCC. The relative contribution of INF, if any, to the combination's overall activity remains a subject of speculation. The utility of bevacizumab as single agent or in combination with reduced doses of IFN await further validation. Except for bevacizumab-IFN combination, current management of mRCC is centered on the sequential application of monotherapy

involving VEGF or mTOR targeted inhibitors. Ongoing and future clinical trials should offer insight into the activity of bevacizumab as a single agent and in combinations with tyrosine kinase and mTOR blockers. Nonetheless, the experience with several bevacizumab-based regimens (eg, bevacizumab/erlotinib) suggests that some combinations may produce prohibitive toxicity that obviates their utility.

Abbreviations

RCC, Renal cell carcinoma; mRCC, Metastatic renal cell carcinoma; IFN, Interferon; VEGF, Vascular Endothelial Growth Factor; pVHL, Von Hippel Lindau protein; HIF-α, Hypoxia-inducible factor—alpha; HDIL-2, High-dose interleukin-2; STAT, Signal transducers and activators of transcription; TTG, Tissue transglutaminase; TKI, Tyrosine kinase inhibitor; mTOR, Mammalian Target of Rapamycin; CALGB, Cancer and leukemia group B; AVOREN, Avastin and Roferon in renal cell carcinoma; Vs, Versus; TTP, Time to progression; ORR, Overall response rate; PFS, Progression-free survival; OS, Overal survival; Mg, Milligram; Kg, Kilogram; MIU, Million international units; MSKCC, Memorial Sloan Kettering Cancer Center.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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