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Treatment of Metastatic Renal Cell Carcinoma

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Abstract

Purpose

To review the treatment of metastatic renal cell carcinoma (RCC), including the use of new targeted therapies.

Methods

A search of MEDLINE (1966 to August 2008) and American Society of Clinical Oncology Meeting abstracts (2005 to May 2008) was preformed using the search terms bevacizumab, everolimus, interferon-alfa (IFN-α), interleukin-2 (IL-2), sorafenib, sunitinib, temsirolimus, and RCC. Articles most pertinent to the treatment of metastatic RCC are reviewed.

Results

The treatment of metastatic RCC has undergone a paradigm shift over the past 5 years from biologic response modifiers to new targeted therapies. Historically, response rates for the biological response modifiers, aldesleukin (IL-2), and IFN-α were approximately 15%. Recently, three targeted agents, sorafenib, sunitinib, and temsirolimus have been approved for the treatment of RCC. Additionally, bevacizumab has been investigated and shown to increase progression free survival in RCC. IL-2 remains the only agent to induce complete, durable remissions; however, many patients are not eligible for this therapy. Newer agents (sorafenib, sunitinib, and temsirolimus) have shown to be superior to IFN-α or placebo and bevacizumab combined with IFN-α has shown activity when compared to IFN-α alone. Unlike IL-2, the greatest benefit obtained with targeted therapies is in achieving stable disease (SD). Despite their benefit, targeted therapies have never been compared with each other in clinical trials and choosing the most appropriate agent remains challenging. To date, the optimal sequence or combination of treatments has not been defined; however, everolimus has recently demonstrated activity in patients progressing on targeted therapy.

Conclusions

IL-2 remains the most active regimen in inducing complete responses; however, its use is accompanied by substantial morbidity and is limited to those with a good performance status. Targeted therapies are also efficacious in the treatment of RCC, with the major benefit being induction of SD. Future research will better define the sequencing of therapies, as well as, explore the activity of novel combination regimens.

Background

Primary kidney cancers comprise approximately 3.8% of malignancies with an estimated 54,390 new cases and 13,010 deaths expected in 2008 [1]. Additionally, the rate of kidney cancer has increased over the past 65 years by 2% per year [2]. When compared to other malignancies, kidney cancer is the seventh most common cancer diagnosis in men and the ninth most common in women, with the peak incidence occurring in the sixth decade [1, 2]. Renal cell carcinoma (RCC) represents 90% of kidney cancers and 30% of persons affected present with metastatic disease [3, 4]. It has been reported that of these, 85% are clear cell carcinomas with the remaining 15% being papillary, chromophobe, and collecting duct carcinomas [2].

Risk factors for developing RCC include smoking, obesity, hypertension, cystic kidney disease, and genetic abnormalities [5]. Most patients with clear cell RCC have mutations of the von Hippel–Lindau (VHL) tumor suppressor gene resulting in cell signaling abnormalities [5]. Under normal conditions, VHL proteins complex with hypoxia inducible factor (HIF) 1-α and 2-β, leading to degradation. However, in its absence, HIF 1-α and 2-β complex together leading to production of growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor α. These growth factors activate cell surface growth factor receptors setting off intracellular signaling pathways, ultimately ending in angiogenesis and proliferation of malignant cells. Additional gene abnormalities in the MET gene and Birt–Hogg–Dubé gene appear to contribute to the pathogenesis of papillary and chromophobe carcinoma, respectively [5].

Metastatic RCC carries a fairly grim prognosis with approximately 10% survival at 5 years [6]. In a report examining prognostic factors in 670 patients with metastatic RCC, the median survival was 10 months [7]. Prognostic factors associated with short survival from this study as well as other similar research includes a Karnofsky performance score ≤70, serum lactate dehydrogenase level >1.5 × upper limit of normal, hemoglobin less than the lower limit of normal, corrected calcium level >10 mg/dl, and <1 year from diagnosis to the start of treatment. By this model, the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score to predict survival was developed and utilized in clinical trials to delineate patients at low risk (no risk factors), intermediate risk (1–2 risk factors) and poor risk (>2 risk factors) [8].

The objective of this article is to familiarize the clinician with the treatment of metastatic RCC, including the use of new targeted agents. As more data become available with targeted therapies and more clinical settings are investigated, the uses of these agents are increasing. Additionally, this shift from traditional therapies to targeted therapies has occurred in many other malignancies. With expanded use, it is important that clinicians be familiar with the role of immunotherapy and targeted therapy in the treatment of RCC, as well as their unique adverse effect profiles.

Literature review

A search of MEDLINE (1966 to August 2008) was preformed using the search terms bevacizumab, everolimus, interferon-alfa (IFN-α), interleukin-2 (IL-2), sorafenib, sunitinib, temsirolimus, and RCC. Review articles, clinical trials, and case reports were identified, and references of these articles were reviewed for additional reports. American Society of Clinical Oncology Meeting

abstracts (2005 to May 2008) were also reviewed. Articles most pertinent to the treatment of metastatic RCC are reviewed here.

Treatment

Overview

Consistent with the short survival associated with metastatic RCC, this malignancy is relatively unresponsive to traditional chemotherapeutic agents [9]. Until recently, patients were left with few options including the biologic response modifiers IL-2 and IFN-α. Development of new targeted therapies led to the approval of three novel agents as well as research into a new paradigm of therapies for RCC. Newly approved agents have quickly moved their way into practice as first and second-line therapies for metastatic RCC. To better understand the role of these new agents, it is imperative to first explore the activity of their predecessors.

Biologic response modifiers

Interleukin-2

Interleukin-2 is an autocrine factor with several immunoregulatory properties that influence the activity of natural killer cells, lymphokine-activated killer cells, and T cells. Recombinant human IL-2, known as aldesleukin, was approved by the Food and Drug Administration (FDA) in 1992 on the basis of a review of 225 patients enrolled in seven different phase II trials of bolus high-dose IL-2 in metastatic RCC [10]. Five of the trials utilized what became the FDA-approved dose, 600,000 IU/kg/dose, administered intravenously over 15 min every 8 h for 14 consecutive doses over 5 days, as tolerated. After 5–9 days of rest, treatment is repeated using the same dosage and administration schedule. The course (two treatment periods separated by 5–9 days of rest) is repeated in 6–12 weeks if there is evidence of tumor regression or stabilization. Two trials utilized a slightly higher dose, 720,000 IU/kg/dose, on the same schedule as above. 85% of the patients previously underwent nephrectomy. The overall response rate (RR) in 255 patients from the seven studies combined was 14% with 5% complete responses (CRs) and 9% partial responses (PRs). Median duration of response of all responders was 20.3 months and 19 months for patients with a PR. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was the only predictive prognostic factor for response to IL-2 with those scoring 0 at baseline having twice the RR as those scoring 1. Subsequent follow-up data showed median survival for all 255 patients was 16.3 months, and the median survival for complete responders had not been reached after more than 80 months of follow-up [11]. However, substantial toxicity is associated with high-dose IL-2 therapy. Capillary leak syndrome, a dose-limiting toxicity, is characterized by weight gain, arrhythmias, hypotension, fluid retention, pulmonary congestion, oliguria, and renal insufficiency. This is reversible, but requires intense monitoring and possibly the use of vasopressor support to maintain blood pressure. Influenza (flu)-like syndromes, such as fever and chills, are frequent. Other side effects include neurologic and neuropsychiatric, hepatotoxicity, transient cytopenia, and skin rash. Drugs with nephrotoxic, myelotoxic, cardiotoxic, or hepatotoxic effects should be used cautiously with IL-2 due to the increased toxicity in these organs. The use of corticosteroid with IL-2 should be avoided since it may decrease the antitumor efficacy of IL-2 due to inhibitory effects on the immune system [12].

Given the substantial toxicity of high-dose IL-2, interest shifted to utilizing lower doses in the metastatic setting. Based on promising results of phase II trials, two phase III trials were undertaken [13, 14]. The first trial compared high-dose (720,000 IU/kg, *n* = 156) or low-dose (72,000 IU/kg, *n* = 150) IL-2 both given IV every 8 h to a maximum of 15 doses [13]. An additional subcutaneous IL-2 arm of the study was added after study initiation (250,000 IU/kg/dose 5 days/week for the first week then 125,000 IU/kg/dose 5 days/week for the next 5 weeks, *n* = 94). Each treatment was repeated after 7–10 days of rest and the entire course was repeated 2 months from the initiation of the first treatment. When comparing high-dose IV and low dose IV regimens, the CR and PR rates were higher with the high-dose regimen (7% CR vs. 4% CR, 14% PR vs. 9% PR, respectively, *P* = 0.048); however, there was no difference in overall survival (OS). Subcutaneous IL-2 had a RR comparable to low dose IV IL-2 (10%); however when compared to high-dose IL-2 a significant difference was present (*P* = 0.033). Among the subgroup of patients achieving a CR, those who received high-dose IL-2 had a significantly longer OS (*P* = 0.04). Overall, patients receiving low-dose IL-2 had fewer adverse effects, especially hypotension, confusion, malaise, and thrombocytopenia. The second phase III trial compared high-dose IL-2 (600,000 IU/kg IV every 8 h days 1–5 and 15–19, maximum 28 doses, *n* = 96) to the combination of subcutaneous IL-2 (5,000,000 IU/m^2 every 8 h for three doses then 5 days/week for 4 weeks) and IFN-α (5,000,000 IU/m^2 thrice weekly for 4 weeks, *n* = 96) [14]. Patients were given a maximum of three cycles of high-dose IL-2 or six cycles of the IL-2/IFN-α combination. There was a significant advantage in RR with high-dose IL-2 compared to those receiving the combination (23.2% vs. 9.9%, respectively, *P* = 0.01). Although not statistically significant, the CR rate was higher with high-dose IL-2 (8.4% vs. 3%, *P* = 0.214). Median survival was also not significantly different between high-dose and combination treatment (17 months vs. 13 months, respectively, *P* = 0.211). Like the prior study, adverse effects were less with the low-dose IL-2. Given the results of these two trials, high-dose IL-2 appears to be more active than lower dose regimens. The lack of a survival benefit for high-dose therapy in these trials may be explained by the relatively small size of the group responding to treatment which would require much larger trials to prove superiority.

In spite of the fact that IL-2 offers the chance for a durable CR, many are not eligible for such a treatment. In general, patients should have a good performance status, good pulmonary, renal, and hepatic function, and be without any significant coronary artery disease. Ineligible patients should be considered for other available systemic treatments described later. Though not as active as high-dose IL-2, low-dose IL-2 ± IFN-α has the ability to produce a response and may be considered given the activity described above.

Interferon-α

The interferons are natural glycoproteins with antiviral, antiproliferative, and immunomodulatory properties. IFN-α, originally derived from leukocytes and now available via recombinant technology, has produced RRs of approximately 15% and response durations of 4–6 months [15]. IFN-α is not approved by the FDA for treatment of RCC; however, it has been widely used for the past 20 years. A single institution trial of 159 patients with RCC found IFN-α2a to achieve a 10% overall RR with a median survival duration of 11.4 months and a 5-year survival rate of 3% [16].

Predictors of good response to IFN-α therapy include patients with good performance status, prior nephrectomy, no prior therapy, and metastases confined to the lungs and mediastinal lymph nodes [17]. Early studies have also compared the combination of IFN-α and chemotherapy with chemotherapy alone and IFN-α monotherapy with medroxyprogesterone [18, 19]. These studies showed a survival advantage with INF-α both when added to vinblastine (median survival 67.6 weeks IFN-α + chemotherapy vs. 37.8 weeks chemotherapy, $P = 0.0049$) and when utilized as monotherapy (median survival 8.5 months IFN-α vs. 6 months medroxyprogesterone, hazard ratio (HR) for death 0.72, $P = 0.017$). A Cochrane Review of immunotherapy in advanced renal cancer is also available to suggest a benefit in survival with IFN-α compared to controls [20]. Based on four comparative studies ($n = 644$) the odds ratio for death at 1 year was 0.56 (95% CI 0.40–0.77) and the pooled overall HR for death was 0.74 (95% CI 0.63–0.88). Based on these results, it was concluded that IFN-α offers a modest survival benefit when compared to controls.

Despite the activity of IFN-α, the optimal dose is not defined. The most commonly used schedules are 9–10 million units per day or 10–18 million units three times per week, given subcutaneously or intramuscularly [15]. The optimal duration of IFN-α treatment has also not been established. Most investigators recommend treatment for at least 3 months, with a maximum duration of 1 year in responders [15]. The toxicities experienced with IFN-α vary directly with the dose, schedule, and patient characteristics. The most common acute toxicities are flu-like syndromes consisting of fever, chills, headaches, myalgias, nasal congestion, dizziness, and tachycardia. Premedication with acetaminophen plus an antihistamine and administering IFN-α at bedtime may help alleviate these symptoms. When increasing doses, nausea, diarrhea, anorexia, liver dysfunction, and mild pancytopenia are not uncommon. IFN-α interacts with several drugs and caution should be exercised when administering IFN-α therapy in combination with other myelosuppressive agents such as zidovudine. Concomitant use of IFN-α and theophylline decreases theophylline clearance, and has resulted in a doubling of theophylline serum concentrations [21].

Targeted therapy

Tyrosine kinase inhibitors

Small molecule tyrosine kinase inhibitors (TKIs) were the first targeted therapies approved for the treatment of RCC. They bind receptor tyrosine kinases located on the intracellular domain of cell surface growth factor receptors, blocking intracellular signaling, and therefore promoting tumor shrinkage. Sorafenib and sunitinib, the two TKIs with FDA approved labeling for the treatment of RCC, block VEGF receptor (VEGFR) intracellular signaling and act as potent antiangiogenic agents. Both are given orally and share many commonalities; however, differences do exist between the two agents.

Sorafenib

Sorafenib (BAY 43-9006, Nexavar®), approved in 2005, is a multikinase inhibitor which was designed as a c-Raf and b-Raf inhibitor. The Ras/Raf signaling pathway is a mediator of tumor cell proliferation and angiogenesis [22]. Sorafenib also inhibits several tyrosine kinases on the intracellular domain of VEGFR1, VEGFR2, VEGFR3, PDGF receptor β, FMS-like tyrosine kinase 3, stem cell factor receptor (KIT), and the glial cell-line derived neurotrophic factor receptor

(RET) (Fig. 1) [23]. Sorafenib is recommended to be given on an empty stomach at a dose of 400 mg orally twice daily [23]. Sorafenib is a substrate for metabolism by cytochrome P450 (CYP) 3A4 and uridine diphosphate glucuronosyltransferase (UGT) 1A1. Sorafenib is a strong inhibitor of UGT1A1, UGT1A9, CYP2B6, CYP2C8, and CYP2C9 and a moderate inhibitor of CYP2C19, CYP2D6, and CYP3A4. Sorafenib can significantly increase the exposure to substrates of UGT1A1 (irinotecan), as well as other hepatically metabolized medications such as docetaxel and doxorubicin. In addition, bleeding and INR elevations have occurred in some patients taking warfarin and sorafenib concurrently [23]. When given concomitantly with ketoconazole, a strong CYP3A4 inhibitor, sorafenib disposition was not altered; however, administration with a strong CYP3A4 inducer (rifampin), resulted in a significant (37%) reduction in sorafenib's area under the plasma concentration vs. time curve (AUC) [23]. A dose increase may be considered based on clinical judgment if concomitant administration with a strong CYP3A4 inducer cannot be avoided [23]. Patients need to be monitored closely for adverse effects if a dose increase is undertaken. Dose adjustments to 400 mg daily or every other day should be instituted as needed based on the severity toxicity.

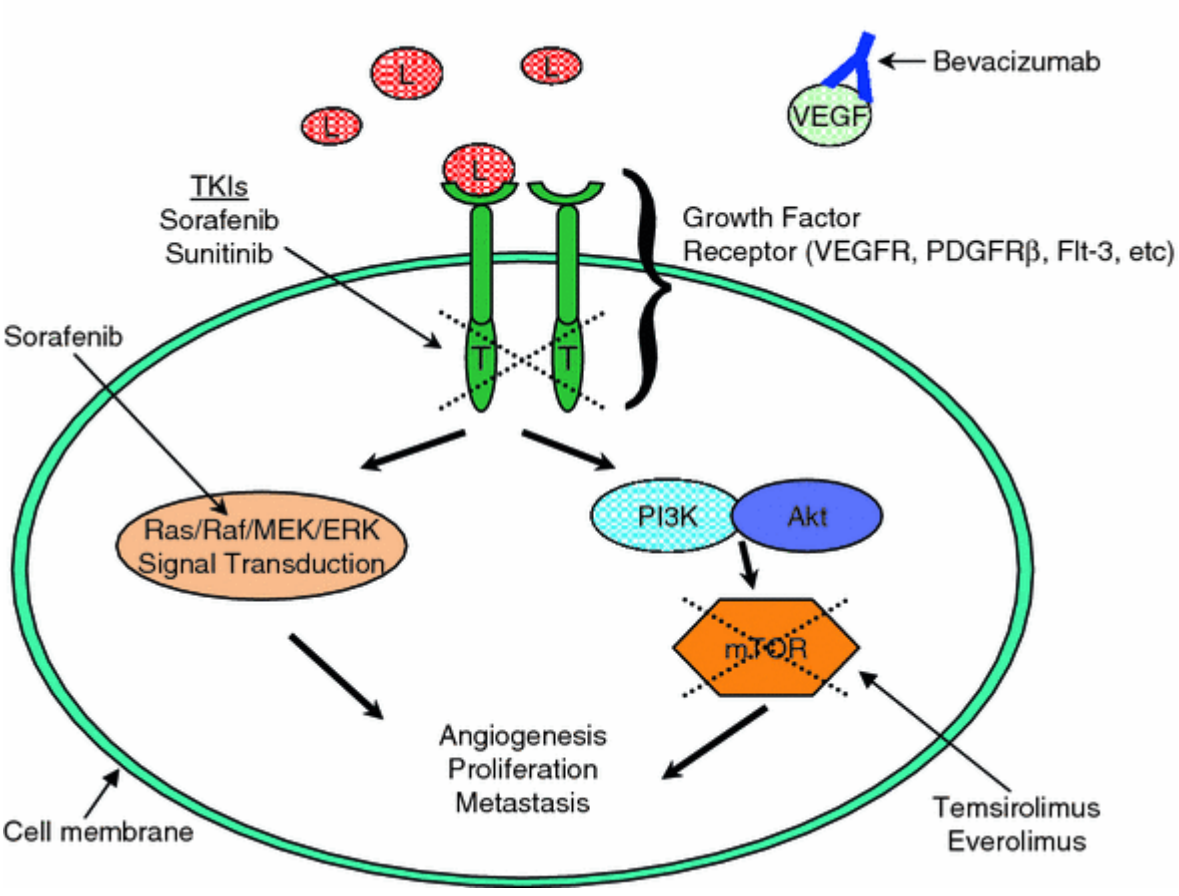

Figure 1 Mechanism of action of targeted therapies in renal cell carcinoma. Flt-3 FMS-like tyrosine kinase 3, L ligand, mTOR mammalian target of rapamycin, PDGFRβ platelet-derived growth factor receptor β, PI3 K phosphatidylinositol 3 kinase, T tyrosine kinase, T

FDA approval of sorafenib was largely based on a multicenter, randomized, double-blind phase III trial, known as Treatment Approaches in RCC Global Evaluation Trial (TARGET), comparing

sorafenib 400 mg twice daily to placebo in 903 patients with previously treated metastatic clear cell RCC [24]. Inclusion criteria included an ECOG performance status of 0 or 1, adequate bone marrow, coagulation, liver, pancreatic, and renal function, and intermediate or low MSKCC prognostic score. Patients with a life expectancy <12 weeks, brain metastases or previous treatment with VEGF inhibitors were excluded. Three years after study initiation, the protocol was amended to allow for those placebo patients still on study to crossover to the sorafenib group after progression. Overall, sorafenib was shown to be more efficacious than placebo with a 10% RR and a 56% reduction in risk of progression [progression free survival (PFS) 5.5 vs. 2.8 months] in second-line treatment of RCC (Table 1). Despite this increase in PFS, sorafenib failed to significantly increase OS according to the O'Brien–Fleming boundaries (19.3 months vs. 15.9 months, $P = 0.02$).

Reference	Treatments	Patient Population	Design/Endpoint	Efficacy				Adverse Effects					
								Any grade (≥30%)[a]			Grades 3 & 4 (≥5%)[a]		
Sorafenib													
TARGET trial	Sorafenib	Previously	Phase III		Placebo	Sorafenib	P		Placebo	Sorafenib		Placebo	Sorafenib
Escudier B et	400 mg BID	treated RCC	multicenter,	OS	14.7 m	NR	-	Diarrhea	13%	43%	HFS	0	6%
al. (2007)[24]	(N= 451)		randomized,	PFS	2.8 m	5.5 m	<.001	Rash	16%	40%	Fatigue	4%	5%
	vs.	Low risk:	double-blind,	OS after	15.9 m	19.3 m	0.02[b]	Fatigue	28%	37%			
	Placebo (N=	49%	placebo-	crossover				HFS	7%	30%			
	452)	Intermediate	controlled trial	CR	0	1 pt	<.001 for						
		risk: 51%		PR	2%	10%	CR + PR						
			Primary	SD	53%	74%							
			endpoint: OS										
Gollob JA et	Sorafenib	63%	Phase II	CR: 5%				Fatigue (90%), Anorexia (78%), Anemia (75%),			↑PO_4 (37%), Neutropenia (25%), Rash (13%),		
al. (2007)[25]	400 mg BID	previously	multicenter,	PR: 28%				Diarrhea (75%), Rash (70%), Nausea (65%),			Fatigue (13%), HFS (10%), ↑ lipase (8%), Anemia		
	+ IFN-α 10	untreated,	open-label trial	SD: 45%				↓Ca^{2+}/↓PO_4 (65-73%), Weight loss (63%),			(8%), Syncope (5%)		
	MU TIW as	88% clear		Median duration of response: 12 m				Alopecia (60%), Thrombocytopenia (55%),					
	1st line	cell RCC	Primary	Median OS: NR				Fever/chills (52-55%), Neutropenia (51%),					
	treatment		endpoint: RR and					Mucositis (48%), ↑ lipase (45%), ↑ transaminase					
	(N=40)		tolerability					(43%), Headache (40%), Myalgia/Arthralgia (37-40%), ↑ albumin (40%), Dyspnea (33%), Bleeding (30%)					
Ryan CW et	Sorafenib	Previously	Phase II	CR: 1 patient				Fatigue (90%), Anorexia (71%), Anemia (66%),			Fatigue (29%), Diarrhea (16%), Anorexia (10%)		
al. (2007)[26]	400 mg BID	untreated	multicenter,	PR: 18%				Diarrhea (63%), Nausea (63%), Rigors/chills			Arthralgia (8%), Depression (6%)		
	+ IFN-α 10	clear cell	open-label trial	SD: 39%				(63%), Fever (56%),			Weight loss (6%), Nausea (5%)		
	MU TIW	RCC		Median duration of response: 8 m				↑ALT/AST (44-53%), Thrombocytopenia (44%),			Anemia (5%)		
	(N= 62)		Primary	Median PFS: 7 m				Rash (39%), Taste alteration (39%), Weight loss			Thrombocytopenia (5%)		
			endpoint: RR					(35%), Dry skin (34%)			↑ ALT (5%)		
Szczylik C et	Sorafenib	Previously	Phase II trial		IFN-α	Sorafenib	P	Rash, HFS, diarrhea			Not reported		
al. (2007)[27]	400 mg BID	untreated		PFS	5.6 m	5.7 m	-						
	(N=97)	clear cell	Crossover to	CR+PR	5%	9%	-						
	vs.	RCC	sorafenib or	CR+PR+									
	IFN-α 9 MU		sorafenib dose	SD	64%	79%							
	TIW (N=92)		escalation at										
			progression										
			Primary										
			endpoint: PFS										
Sunitinib													
Motzer RJ et	Sunitinib 50	Previously	Phase III		IFN-α	Sunitinib	P		IFN- α	Sunitinib		IFN- α	Sunitinib
al. (2007)[28,	mg daily 4	untreated	multicenter,	PFS	5 m	11 m	<.001	Neutropenia	46%	72%	↑Lipase	6%	16%
29]	weeks on, 2	clear cell	randomized trial	OS	21.8 m	26.4 m	0.051	Anemia	64%	71%	↑Uric acid	8%	12%
	weeks off	RCC		CR	0	0		↑Creatinine	49%	66%	Neutropenia	7%	12%
	(N= 375)		Primary	PR	6%	31%	<.001	↑Plt	21%	65%	↑Plt	0	8%
	vs.	Low risk:	endpoint: PFS	SD	49%	48%		Diarrhea	12%	53%	Hypertension	1%	8%
	IFN-α 9 MU	36%						↑Lipase	42%	52%	Fatigue	12%	7%

Reference	Treatments	Patient Population	Design/Endpoint	Efficacy	Adverse Effects					
					Any grade (≥30%)[a]			Grades 3 & 4 (≥5%)[a]		
	TIW (N= 375)	Intermediate risk: 57.5% Poor risk: 6.5%			↑ALT/AST	39/34%	46/52%	↑Amylase	3%	5%
					Fatigue	51%	51%	↑PO_4	6%	5%
					Nausea	33%	44%	HFS	0	5%
					↑Alkaline phosphatase	35%	42%	Diarrhea	0	5%
					↑Uric acid	31%	41%			
					↑PO_4	32%	36%			
					↑Amylase	28%	32%			
Motzer RJ, et al. (2006) [30]	Sunitinib 50 mg daily 4 weeks on, 2 weeks off as second-line therapy (N=63)	Previously treated, cytokine-refractory RCC	Phase II trial Primary endpoint: ORR	ORR: 40% SD: 25% TTP: 8.7 m	Lymphopenia (72%), Neutropenia (45%), Fatigue (38%), Anemia (37%)			Lymphopenia (32%), ↑Lipase (21%), Neutropenia (13%), Fatigue (11%), Anemia (10%), ↑Amylase (8%)		
Motzer RJ et al. (2007) [31]	Sunitinib 50 mg daily 4 weeks on, 2 weeks off as second-line therapy (N=106)	Previously treated, cytokine-refractory RCC	Phase II Multicenter, open-label trial Primary endpoint: RR	ORR: 33% Median duration of response: 14 m Median TTP: 10.7 m OS: 23.9 m	Neutropenia (45%)			↑Lipase (17%), Neutropenia (16%), Fatigue (11%), HFS (7%), Thrombocytopenia (6%), Hypertension (6%), Stomatitis (5%)		
Temsirolimus										
Hudes G et al. (2007)[32]	IFN-α 18 MU TIW (N=207) vs. temsirolimus 25 mg qwk (N= 209) vs. temsirolimus 15 mg qwk + IFN-α 6 MU TIW (N=210)	Previously untreated RCC with poor prognosis 80% with clear cell RCC Intermediate risk: 26% Poor risk: 74%	Phase III multicenter, open-label trial Primary endpoint: OS	OS: IFN 7.3 m; Tem 10.9 m; IFN+Tem 8.4 m; P=0.008 PFS: IFN 3.1 m; Tem 5.5 m; IFN+Tem 4.7 m; P<.001 RR: IFN 4.8%; Tem 8.6%; IFN+Tem 8.1% RR + SD: IFN 15.5%; Tem 32.1%; IFN+Tem 28.1%	Asthenia 64% 51% 62% Rash 6% 47% 21% Anemia 42% 45% 61% Nausea 41% 37% 40% Anorexia 44% 32% 38%			Anemia 22% 20% 38% Asthenia 26% 11% 28% Hyperglycemia 2% 11% 6% Dyspnea 6% 9% 10% Pain 2% 5% 6% Infection (5%) 4% 5% 11%		
Bevacizumab										
Escudier B et al. (2007)[33]	Bevacizumab 10 mg/kg q2wk + IFN-α2a 9 MU TIW (N=327) vs.	Previously untreated clear cell RCC Low risk: 28% Intermediate	Phase III multicenter, randomized, double-blind, placebo-controlled trial	OS: IFN 19.8 m; IFN+Bev NR; P PFS: IFN 5.4 m; IFN+Bev 10.2 m; P <.001 CR: IFN 2%; IFN+Bev 1% PR: IFN 11%; IFN+Bev 30% CR+PR: IFN 13%; IFN+Bev 31%; P <.0001 SD: IFN 50%; IFN+Bev 46%	Pyrexia 43% 45% Anorexia 30% 36% Bleeding 9% 33% Fatigue 27% 33% Asthenia 28% 32% HTN 9% 26%			Fatigue 8% 12% Asthenia 7% 10% Proteinuria 0 7% Anemia 6% 3%		

Table 1 Summary of targeted therapy clinical trials

ALT alanine transaminase, *AST* aspartate transaminase; *Bev* bevacizumab, *CR* complete response, *HFS* hand-foot syndrome, *HR* hazard ratio, *IFN-α* interferon alpha, *MU* million units, *NR* not reached, *ORR* objective response rate, *OS* overall survival, *PFS* progression free survival, *PR* partial response, *TTP* time to progression, *RCC* renal cell carcinoma, *SD* stable disease, *Tem* temsirolimus, *TIW* three times weekly

[a]Incidence of adverse effects in the targeted therapy group

[b]Did not reach predetermined definition of statistical significance according to the O'Brien–Fleming boundaries

Recent trials have investigated use of sorafenib in combination with IFN-α as first-line treatment of RCC. A phase II trial of sorafenib 400 mg twice daily plus IFN-α 10 million units three times weekly included 40 patients, 63% were previously untreated and 88% had clear cell carcinoma [25]. Patients who had previously received interferon were excluded. Another phase II trial investigated the same combination of sorafenib and IFN-α in 67 patients as first-line treatment of clear cell carcinoma [26]. These early trials showed sorafenib was active in the first-line setting (Table 1).

The most recent phase II trial assessed first-line treatment in 189 patients with clear cell carcinoma who were randomly assigned to receive sorafenib 400 mg twice daily or IFN-α 9 million units three times weekly [27]. At disease progression, patients receiving sorafenib were permitted to escalate the sorafenib dose to 600 mg twice daily. Patients initially assigned to receive IFN-α were allowed to crossover to the sorafenib 400 mg group at disease progression. Of the patients enrolled, 44 had their dose escalated and 50 crossed over from IFN-α to sorafenib. Though the trial did not show a difference in its primary endpoint (PFS), it did indicate that sorafenib alone has noteworthy activity as first-line therapy for RCC (9% RR), requiring further exploration (Table 1).

Sunitinib

Sunitinib (SU11248, Sutent®), approved in 2006, is the second TKI marketed in the United States for the treatment of RCC. It inhibits the same tyrosine kinases as sorafenib plus the colony stimulating factor receptor Type I, but it does not inhibit Raf (Fig. 1) [36]. The recommended dosing schedule is 50 mg daily orally for 4 weeks, followed by 2 weeks off treatment (6-week cycles) and it may be given without respect to food intake [36]. Drug interactions are possible with sunitinib as it also is metabolized via CYP3A4. The CYP3A4 inhibitor ketoconazole increased C_{max} and AUC of sunitinib by 49 and 51%, respectively. Likewise, the inducer rifampin decreased the C_{max} and AUC of sunitinib by 23 and 46%, respectively. In contrast, sunitinib does not significantly inhibit nor induce any CYP isoenzymes. To prevent significant interactions, it is recommended that coadministration with strong CYP3A4 inducers or inhibitors be avoided. If coadministration must occur, doses should be adjusted to 37.5 mg/day in the presence of a strong CYP3A4 inhibitor or 87.5 mg/day in the presence of a strong CYP3A4 inducer. Moreover, sunitinib doses should be decreased by 12.5 mg increments to a minimum of 25 mg based on tolerability.

Sunitinib's efficacy as second-line therapy for patients with a prior nephrectomy and cytokine-refractory RCC was investigated in two open-label, single-arm, multicenter phase II trials [30, 31]. Sixty-three patients were enrolled in the first trial and 106 patients were enrolled, of which 105 were evaluable for efficacy, in the second trial. Both trials demonstrated that sunitinib is active in the second-line setting with RRs of 40 and 33% and PFS of 8.7 and 8.8 months (Table 1). Based on the results of these studies, FDA granted accelerated approval for sunitinib. A phase III trial confirmed the results of the phase II studies and compared sunitinib with IFN-α in 750 patients with untreated metastatic clear cell RCC, an ECOG performance status of 0 or 1, and adequate bone marrow, coagulation, hepatic, renal, and cardiac function [28]. Patients with brain metastases or cardiovascular events or disease during the preceding 12 months were excluded. Median duration of treatment was 11 months in the sunitinib group and 4 months in the IFN-α group.

Patients assigned to receive sunitinib achieved a median PFS of 11 months, which was more than double the 5-month PFS observed in the IFN-α group (HR: 0.42). OS difference between the groups was borderline for statistical significance possibly due to crossover to sunitinib after progression on IFN-α alone (26.4 months sunitinib vs. 21.8 months IFN-α, $P = 0.051$) [29]. Results of this study proved the superiority of sunitinib over IFN-α as first-line treatment for clear cell RCC (Table 1).

Sorafenib and sunitinib adverse effects

Adverse effects commonly associated with sorafenib and sunitinib include: diarrhea, nausea, vomiting, fatigue, rash, hand-foot syndrome, and leucopenia. See Table 1 for common adverse effects observed in trials evaluating sorafenib and sunitinib. Uncommonly, both agents have been reported to cause adverse events such as chemical pancreatitis and reversible leukoencephalopathy. Sunitinib can cause QT prolongation with Torsades de Pointe as well as thyroid and adrenal dysfunction and patients should be monitored for such throughout therapy. Though generally milder than adverse effects associated with cytotoxic chemotherapy and immunomodulators, these adverse effects may decrease a patient's quality of life and can result in dose interruption or discontinuation of drug, compromising benefits of treatment.

Hypertension, bleeding, wound healing complications, gastrointestinal perforation, and adverse cardiac effects are associated with inhibition of angiogenesis and have been described with both agents. Based on FDA approved labeling, bleeding occurred in 15 and 30% of those receiving sorafenib and sunitinib, respectively [23, 36]. Gastrointestinal perforation occurs rarely (<1%) and, although not formally investigated, wound healing complications can occur. Patients should be monitored for bleeding and gastrointestinal perforation during treatment and invasive surgical procedures should be avoided. Moreover, the bleeding risk raises concern about utilizing these agents in patients with brain metastases. To date brain metastases have been part of the exclusion criteria for trials. A 7% mortality rate due to intracerebral hemorrhage (ICH) has been described in a small, single institution report of sorafenib and sunitinib use [37]. Four of the five patients who died because of the ICH had known brain metastases. This high rate of ICH may be explained by the high incidence of uncontrolled hypertension in patients experiencing an ICH (four of the five). In contrast to the prior report, multiple descriptions are available from expanded access trials which report central nervous system bleeding at no more than 1% with CNS tumor involvement approaching 8% [38]. To date there are no specific recommendations for or against their use in this setting and caution should be exercised. Patients with uncontrolled hypertension should wait until their pressure is under control. Warfarin should also be avoided in patients receiving antiangiogenic therapy given the pharmacodynamic interactions with the possibility of additive or synergistic bleeding effects and the pharmacokinetic interaction between sorafenib in which warfarin metabolism is inhibited. If a patient is not a candidate for alternative anticoagulants, frequent monitoring is necessary, especially with sorafenib.

Hypertension and cardiotoxicity associated with these TKIs were recently investigated. In a meta-analysis examining the incidence and risk of hypertension in 4,599 patients receiving sorafenib in nine studies, the incidence of hypertension was 23.4% and grade 3 (requiring intense treatment) and grade 4 (life threatening) hypertension occurred in 5.7% of patients [39]. The overall relative

risk for the development of hypertension during sorafenib treatment was 6.11. Likewise, sunitinib has been associated with a 22.5% incidence of hypertension with a relative risk of 3.9 [39]. Blood pressure should be closely monitored during the initial weeks after starting sorafenib and sunitinib. Management of hypertension can be achieved by adding an antihypertensive agent and/or dose reduction of sorafenib/sunitinib. However, in the event of either uncontrollable hypertension despite interventions or hypertensive crisis, these agents should be held until blood pressure is well controlled.

A review of 75 patients who received sunitinib for gastrointestinal stromal tumors evaluated its propensity to cause cardiotoxicity [40]. Patients with a history of congestive heart failure (CHF) or baseline left ventricular ejection fractions (LVEF) ≤50% were not eligible. Among enrolled patients, 11% experienced a cardiovascular event (myocardial infarction, heart failure, or death from cardiovascular cause). Risk factors for developing a cardiovascular event were a history of hypertension and coronary artery disease. CHF was detected in 8% of patients and an additional 47% experienced a decrease in LVEF of at least 10%. Overall, there was a mean reduction of 5% in the LVEF during four cycles of sunitinib. In patients who received sunitinib for RCC, 4% experienced a decrease in the LVEF of >20%, and 21% had a decline to below the lower limits of normal [36]. Sorafenib has also been associated with myocardial ischemia/infarction (2.9%) and CHF (<1%) [23]. Patients with a history of cardiac disease and no alternative treatment options should be monitored closely for the development of cardiac adverse events during sorafenib and sunitinib treatment. Patients developing significant or worsening cardiotoxicity should have the drug discontinued.

Hand-foot syndrome and other dermatologic reactions have been associated with sorafenib and sunitinib. Among nine patients who received sorafenib, seven developed hand-foot skin reactions (one grade 1, three grade 2, three grade 3) [41]. The typical presentation included tingling and burning which progressed to erythematous patches and then large tense blisters. Another study investigating the incidence of dermatologic adverse events induced by sunitinib by pooling results from published trials and abstracts reported skin discoloration in 24%, rash in 13%, dermatitis in 8%, and hand-foot skin reactions in 19% (5% grades 3 or 4) [42]. Patients who develop these skin reactions should receive supportive care, including skin hydration and keratolytics to reduce epidermal thickness. Dose adjustments are recommended in patients experiencing dermatologic adverse effects and if dermatologic reactions do not resolve, it may be necessary to interrupt treatment.

Temsirolimus

Temsirolimus (CCI-779, Torisel®) most recently received FDA approval for the treatment of advanced RCC. It inhibits the mammalian target of rapamycin (mTOR), which is regulated by upstream kinases, including phosphatidylinositol 3 kinase/Akt [43]. Temsirolimus halts signaling at the mTOR by binding the FK binding protein 12, inhibiting its ability to phosphorylate P70S6 k and 4E-BP1. Interruption of mTOR signaling decreases levels of HIF, VEGF, and other intracellular factors involved in progression of the cell through its cycle (Fig. 1). The approved dose is 25 mg weekly given intravenously [43]. Drug interactions can occur with this agent as it is metabolized by CYP3A4. When given concomitantly with rifampin, there was no effect on

temsirolimus kinetics; however, there was a 65 and 56% reduction in C_{max} and AUC, respectively, of sirolimus, the principal active metabolite. Likewise, administration with ketoconazole increased the sirolimus AUC 3.1-fold and C_{max} 2.2-fold; temsirolimus kinetics remained unchanged. Coadministration of strong CYP3A4 inducers and inhibitors should be avoided. If unavoidable, the temsirolimus dose should be increased to 50 mg when given with a strong CYP3A4 inducer and decreased to 12.5 mg when given with a strong inhibitor of CYP3A4 [43]. Temsirolimus does inhibit CYP2D6 and 3A4; however, when given with desipramine, a CYP2D6 substrate, there were no clinically significant changes in desipramine pharmacokinetics.

In the only phase III trial reported to date, temsirolimus was compared with IFN-α2a and the combination of temsirolimus and IFN-α2a as first-line treatment in 626 patients with metastatic RCC and three or more risk features based on MSKCC prognostic criteria [32]. Patients with neurologically unstable brain metastases were excluded. Eighty percent had clear cell RCC. Compared to IFN-α, temsirolimus monotherapy was associated with an increase in OS (10.9 months vs. 7.3 months, $P = 0.008$), PFS (5.5 months vs. 3.1 months, $P < 0.001$), and RR (8.6% vs. 4.8%) and was better tolerated than IFN-α2a alone (grades 3–4 adverse effects: 69% vs. 85%). The addition of temsirolimus to IFN-α did not add benefit in OS and was associated with an increase in adverse events (grades 3–4 adverse effects: 87%) (Table 1). Compared to studies evaluating sorafenib and sunitinib, the present study evaluated patients with a much poorer prognosis. Overall, 74% of patients were poor risk while none of those in the phase III sorafenib trial and only 6.5% of those in the sunitinib trial were poor risk. Additionally, unlike the sorafenib and sunitinib phase III studies, temsirolimus resulted in a statistically significant OS benefit. Unfortunately, given the difference in study population, results cannot be compared between studies.

Temsirolimus adverse effects

The most common adverse reactions are asthenia, rash, nausea, and anorexia (Table 1). Hypersensitivity reactions are common with temsirolimus and premedication with diphenhydramine or similar histamine-1 receptor antagonist is recommended. Temsirolimus inhibits the production of VEGF and is associated with adverse effects commonly observed in patients who receive antiangiogenic therapy, including hypertension (7%), bowel perforation (1%), and abnormal wound healing (1%) [43]. Surgery should be avoided during treatment and adequate time for wound healing should be allowed before instituting temsirolimus. Sirolimus is the primary active metabolite, and adverse effects occurring in patients receiving temsirolimus which have also been documented with sirolimus include hyperglycemia (89%), hypercholesterolemia (87%), hypertriglyceridemia (83%), immunosuppression, and interstitial lung disease. Cardiac adverse events which are associated with the antiangiogenic TKIs sorafenib and sunitinib have not been observed to date in patients receiving temsirolimus.

Bevacizumab

Bevacizumab (Avastin®), a humanized monoclonal antibody, binds and neutralizes circulating VEGF ligand, preventing activation of the VEGFR (Fig. 1). No drug–drug interactions have been identified with bevacizumab and dosage adjustments are not necessary based on renal or hepatic

function. A double-blind phase III trial randomized 649 patients with clear cell RCC to either bevacizumab 10 mg/kg every 2 weeks plus IFN-α2a 9 million units three times per week or placebo plus IFN-α2a as first-line treatment [33]. Patients were included if they had received a prior nephrectomy or partial nephrectomy, a Karnofsky performance status of 70% or more, normal hepatic, bone marrow, and renal function, and minimal proteinuria at baseline (≤0.5 g/24 h). Exclusion criteria included prior systemic therapy, recent surgery, brain metastases, use of anticoagulants or antiplatelet agents, uncontrolled hypertension, and cardiovascular disease. Median follow-up was 13.3 months in the bevacizumab group and 12.8 months in the placebo group. Due to receipt of TKIs after progression in this trial, median OS may not be an accurate representation of bevacizumab activity; therefore, the primary endpoint was revised to PFS. The combination of bevacizumab and IFN-α2a was more active than IFN-α2a (PFS 10.2 months vs. 5.4 months) in the first-line treatment of RCC in this trial (Table 1). Another phase III trial (CALGB 90206) had a similar design as the aforementioned study, but IFN-α2b was used instead of IFN-α2a [34]. Again, the combination of bevacizumab and IFN-α2b was significantly more efficacious than IFN-α2b alone [time to progression (TTP) 8.5 vs. 5.2 months; RR 25.5% vs. 13.1%, respectively] (Table 1). The activity of bevacizumab monotherapy has also been investigated in a randomized, double-blind, phase II trial [35]. A total of 116 patients were randomized to either placebo or bevacizumab at doses of 3 or 10 mg/kg. The study was closed prematurely due to a significant increase in TTP with high-dose bevacizumab compared to placebo (4.8 months vs. 2.5 months, $P < 0.001$). Low-dose bevacizumab (3 mg/kg) resulted in a difference in TTP of borderline significance (3.0 months vs. 2.5 months, $P = 0.041$). Patient receiving high-dose bevacizumab had a RR of 10%; however, at the last analysis, there was a lack of a difference in OS between groups ($P > 0.20$).

Bevacizumab adverse effects

The addition of bevacizumab to IFN therapy was acceptable in terms of toxicity in most patients with a higher incidence of bleeding, hypertension, and proteinuria (Table 1). Similar to other agents targeting VEGF and angiogenesis, bevacizumab has been associated with hemorrhage (4.7–5.2%), arterial thromboembolism (4.4%), venous thromboembolism (13.6–15.1%), hypertension (8–18%), left ventricular dysfunction (grades 2–4: 1.7%), proteinuria (grades 3/4: 3%), gastrointestinal perforation (0–3.7%), and wound healing complications (0.8%) [44]. Gastrointestinal perforation occurred in 1% of patients in post marketing studies and generally presents as abdominal pain, constipation, emesis, and fever. Due to complications with wound healing, bevacizumab initiation should be delayed at least 28 days after surgery; however, the optimal time between bevacizumab discontinuation and surgery is yet to be determined. Patients who develop ≥2 g/24 h of proteinuria while receiving bevacizumab should have the drug discontinued. Infusion reactions can also occur with bevacizumab (<3%) and are associated with hypertension, wheezing, oxygen desaturation, hypersensitivity, chest pain, rigors, and diaphoresis [44]. Recently, the makers of bevacizumab released information about reports of microangiopathic hemolytic anemia in patients with solid tumors enrolled in a phase I study of the combination of bevacizumab and sunitinib [45].

Sequential targeted agents

Currently available targeted agents involve VEGF pathway inhibition, however, their mechanisms of action differ slightly and there may be a role for sequential use of these agents. Few reports are available suggesting that patients may benefit from use of a targeted agent after progression. In a retrospective trial, 30 patients (93% clear cell carcinoma) receiving sunitinib or sorafenib after progression on prior antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab, volociximab, AG13736, sorafenib, or sunitinib) were evaluated [46]. Overall, ten patients experienced a PR and median TTP was 10.4 months.

An additional report evaluated sorafenib in patients who previously received bevacizumab [47]. This is a subset analysis of patients enrolled in the nonrandomized, open label sorafenib expanded access program. 195 patients were evaluable for response of which 77.5% had stable disease (SD) and 2.5% had PR. Sunitinib was also evaluated in 61 patients with bevacizumab refractory metastatic RCC [48]. The RR was 23% and SD occurred in 57% of patients. This preliminary data suggests there is activity of second-line targeted therapy after progression on another targeted agent.

Combined targeted therapies

Given the differences in mechanisms of action, and the apparent lack of cross resistance described above, combined targeted therapy has been proposed to maximize VEGF inhibition and increase activity of these drugs in patients with metastatic RCC. Data is available suggesting a benefit to combined treatment with targeted therapies. A phase I trial investigated the combination of bevacizumab and sunitinib [49]. Twenty-six patients with metastatic RCC were enrolled with 1 CR, and 12 PRs. Despite the RR, the combination was not well tolerated at full doses; with 10 patients requiring sunitinib dose reductions and 11 withdrew due to toxicity. This increase in toxicity with the combination lead to the warning of microangiopathic hemolytic anemia described above. A phase I trial in 46 patients combining sorafenib and bevacizumab also showed promising results (21 PRs and 23 with SD) with unexpected toxicity [50]. Maximum tolerated doses were sorafenib 200 mg daily and bevacizumab 5 mg/kg every 2 weeks and have been included in a phase II trial. Another Phase I trial investigated the combination of temsirolimus and bevacizumab [51]. Twelve patients with metastatic RCC were enrolled with seven PRs and three with SD. Until more mature efficacy and safety data are available, combination targeted therapy remains investigational.

Discontinuation of targeted therapy

A common question many patients have once placed on a targeted therapy is “How long do I have to take this?” Unfortunately, little data is available to answer the question. Trials presented previously continued treatment until disease progression or unacceptable toxicity. Since the major benefit to these agents is in inducing SD, it is unlikely that discontinuation will be possible. A randomized discontinuation trial is available reporting results of patients randomized to sorafenib and placebo after achieving SD with 12 weeks of sorafenib [52]. Two hundred two patients were enrolled (75% with clear cell carcinoma), of which 65 achieved SD and were randomized (32 sorafenib, 33 placebo). Twelve weeks after randomization, 50% receiving sorafenib remained progression free compared to 18% receiving placebo. PFS was 24 and 6 weeks in those receiving

sorafenib and placebo, respectively. This report confirms the suspicion that patients should remain on targeted therapies until disease progression as progression can occur shortly after discontinuation.

Non-clear cell RCC

Trials evaluating targeted therapies predominantly enrolled patients with clear cell RCC while other histologies were underrepresented. Clear cell carcinoma is closely related to VHL gene mutations which make them susceptible to targeted therapies; however, this pathogenic mechanism is not associated with non-clear cell RCC. Likewise, these malignant subtypes are less likely to respond to treatment with chemotherapy or biologic response modifiers. Data assessing efficacy of targeted therapies in non-clear cell carcinoma is limited, although, early data does suggest that these agents may have some activity. In a multicenter, retrospective review of patients receiving sunitinib and sorafenib for metastatic papillary and chromophobe RCC, 53 patients were evaluated for response [53]. Seventy-seven percent had papillary and 23% had chromophobe histologies with 66% receiving prior therapy. PR occurred in 10% of the patients and SD in 68%. Median PFS was 8.6 months. Among those with papillary carcinoma, two patients receiving sunitinib had a PR. The median PFS was 11.9 months with sunitinib and 5.1 months with sorafenib suggesting more activity with sunitinib. Two patients with chromophobe RCC receiving sorafenib had a PR compared to one receiving sunitinib. All other patients with this histology experienced SD. PFS for chromophobe tumors was 8.9 months in those receiving sunitinib and 27.5 months in those receiving sorafenib which is in direct contrast to that observed in papillary RCC.

A subgroup analysis of non-clear cell RCC in the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial evaluated 212 patients [54]. Histologies included papillary (80.2%), chromophobe (13.7%), collecting duct (4.7%), and oncocytoma (1.4%). PR occurred in 3.4% with papillary and 5.6% with chromophobe RCC. SD was observed in 77% of those with papillary, 88.8% with chromophobe, 60% with collecting duct, and 100% with oncocytoma. Overall, sorafenib was most active in papillary and chromophobe RCC. More mature results, as well as larger phase III trials, will lead to more definitive conclusions in patients with non-clear cell RCC.

Investigational agents

Though the recently approved agents represent an advance in the treatment of RCC, there is much room for improvement. Available agents are only able to prolong OS a few months at most and agents with longer durations of response and greater prolongation of survival continue to be awaited. Additionally, agents without cardiac effects would be useful as all of the targeted agents presently used in RCC except temsirolimus have been associated with adverse cardiac effects. New agents with the characteristics of the ease of oral administration, well tolerability and better efficacy would be greatly beneficial to patients with metastatic RCC. In addition to the approved targeted therapies, others are under investigation. Other targeted therapies being investigated for RCC include axitinib, lapatinib, pazopanib, and RAD001 (everolimus). Axitinib and pazopanib, both TKIs with antiangiogenic properties, have shown promising activity in phase II trials and continue to be investigated for the treatment of RCC [55–57]. Lapatinib, an epidermal growth

factor receptor (EGFR) and HER2 dual TKI approved for the treatment of breast cancer expressing HER2, showed positive results in treating RCC over expressing EGFR. A phase III study evaluated lapatinib vs. hormonal therapy in advanced RCC patients who failed prior therapy [58]. TTP for patients with EGFR over expression was 15.1 weeks vs. 10.9 weeks (P = 0.06) and OS was increased at 46.0 vs. 37.9 weeks (P = 0.02) for lapatinib and hormone therapy, respectively. Everolimus is an oral serine–threonine kinase inhibitor of mTOR similar to temsirolimus. Recently, the results of a phase III trial of everolimus after progression on sorafenib, sunitinib or both in metastatic RCC demonstrated promising results [59]. Patients with clear cell RCC were randomized to either everolimus 10 mg daily (n = 272) or placebo plus best supportive care (n = 138). The majority of the study population was male with a performance status >80. Unlike the population in the temsirolimus study, those enrolled in this study had favorable or intermediate risk scores with only 15% of those in each group having poor risk scores according to MSKCC criteria. The study was halted after the second interim analysis showed that the primary endpoint, PFS, was significantly longer with everolimus (4.0 months everolimus vs. 1.9 months placebo, $P < 0.0001$). Adverse effects occurring significantly more frequently in the treatment arm included stomatitis (40%), infections (10%), and pneumonitis (8%). Everolimus also resulted in significant laboratory abnormalities such as hypercholesterolemia (76%), hypertriglyceridemia (71%), hyperglycemia (50%), lymphopenia (42%), and hyperphosphatemia (32%). Based on these results, the makers of everolimus have submitted a new drug application to the FDA for consideration. Future results from studies with these agents, as well as others undergoing investigation are anticipated to continue the current trend of utilizing targeted therapies for the treatment of RCC.

Treatment of choice

Targeted agents have not been compared in head to head trials which makes choosing an agent difficult. Moreover, the populations enrolled differed from study to study. Though all patients had metastatic RCC and the majority had clear cell histology, MSKCC prognostic scores differed between studies with temsirolimus being investigated in the population with the highest risk. This heterogeneity between studies makes comparing RRs between them problematic. In addition to the difficulties in choosing the initial targeted therapy, few data are available to guide therapy after progression. Retrospective analyses and subgroup analyses suggest moving to another targeted therapy after progression may be beneficial; however, the investigational mTOR inhibitor, everolimus, may become the standard in such a patient if granted FDA approval. Based on available evidence and patient characteristics, the following in Table 2 may be considered reasonable therapy choices in metastatic RCC. IL-2 remains the only treatment known to induce complete and durable remissions, albeit in a minority of patients. Prospective studies are underway to identify patients more likely to respond to IL-2 immunotherapy based on carbonic anhydrase IX expression in the primary tumor and other assessments of immune function and regulation [61]. This study may help to resolve the sequence and selection of available agents for individual patients with metastatic disease. Additionally, drug costs and patient specific insurance coverage must be considered in designing an individualized treatment plan (Table 2).

Table 2

Treatment options for metastatic clear cell RCC and estimated cost

Patient characteristics	Targeted therapy of choice	Approximate average wholesale price [60]
Previously untreated clear cell RCC		
Low or intermediate risk	Sunitinib or bevacizumab + IFN-α	Sunitinib: $7,995/6 weeks; Bev + IFN: $11,435/ 4 weeks[b]
Poor prognosis (high-risk)	Temsirolimus	$5,535/4 weeks
Robust patients with excellent cardiopulmonary reserve	IL-2	600,000 IU/kg: $25,300/cycle[b]
Previously treated clear cell RCC	Sorafenib[a]	$5,960/month

[a]For patients in whom standard doses initially fail, an increase in dose of sorafenib may give responses; patients in whom sorafenib is failing may be treated with sunitinib if not previously used

[b]Based on a 70-kg patient

The treatment of metastatic RCC is challenging, and whenever possible, patients should be directed to approved and controlled clinical trials. This applies as well in the adjuvant treatment of surgically resected RCC, for which no therapy has been found to be of survival benefit.

Conclusions

Interleukin-2 represents the most active first-line drug to date in inducing durable CR; however, many are not eligible for this treatment based on standard eligibility criteria. Targeted therapies represent a significant advance in the treatment of RCC and have been shown to be superior to IFN-α or placebo, with the main benefit being induction of stable disease. Bevacizumab also displayed efficacy in the treatment of RCC when added to IFN-α. Similar to this approach, future treatment strategies for advanced RCC will likely incorporate a combination of molecular approaches, using multi-drug regimens consisting of small-molecule kinase inhibitors with biologic therapies, immunomodulatory therapies, or both.

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