RCCU | 2010 SPECIAL EDITION

Third in a Three-Part Series

Renal Cell Cancer™

U P D A T E

Practical Considerations in the Management of Renal Cell Cancer
Proceedings from a Case-Based CME Symposium

EDITOR
Neil Love, MD

FACULTY
Ronald M Bukowski, MD
Toni K Choueiri, MD
Daniel J George, MD
Robert J Motzer, MD

Special edition focused on the treatment of RCC developed in conjunction with the Florida Cancer Specialists

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Renal Cell Cancer Update

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OVERVIEW OF ACTIVITY

An increased understanding of the biology of renal cell cancer (RCC) coupled with emerging clinical trial data has resulted in the availability of several new therapeutic options for patients. However, the treatment algorithm has become increasingly complex, and the excitement accompanying the explosion of novel agents with proven efficacy in RCC has been somewhat tempered by a full appreciation of the unique tolerability challenges experienced by patients. Thus, practicing oncologists must maintain current knowledge of the benefits and risks of the multiple acceptable treatment approaches. To bridge the gap between research and patient care, this program features a case-based roundtable discussion with leading investigators to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Identify patient characteristics that may help to distinguish the individualized utility of cytoreductive nephrectomy in the era of effective targeted therapies for metastatic renal cell carcinoma (mRCC).
- Apply the results of existing and emerging clinical research to the evidence-based selection of front-line and subsequent therapy for mRCC.
- Develop an approach for the sequencing of therapies for advanced RCC, incorporating biologic response modifiers, tyrosine kinase inhibitors (TKIs), anti-VEGF antibodies and mTOR inhibitors.
- Educate patients with mRCC about the safety and tolerability of multikinase VEGF TKIs, mTOR inhibitors and VEGF monoclonal antibody therapy.
- Recommend supportive measures to enhance the tolerability of targeted therapeutic agents for RCC, including the use of dose reductions, schedule changes or alternative therapies.
- Recall the scientific rationale for and early efficacy of novel investigational compounds demonstrating activity in RCC.
- Counsel appropriately selected patients with RCC about the availability of ongoing clinical trial participation.

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Select commentary from separate, case-based roundtable discussions with Drs Bukowski and George and Drs Choueiri and Motzer in addition to a meeting with these clinical investigators and community oncologists from the Florida Cancer Specialists, a multisite private oncology and hematology practice in western Florida, was excerpted for inclusion in the print monograph.

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EXPECTANT OBSERVATION WITHOUT SPECIFIC ANTITUMOR THERAPY

DR LOVE: Ron, under what circumstances do you believe it is appropriate to observe patients with metastatic disease?

DR BUKOWSKI: We watch patients with indolent disease related to the growth pattern of the cancer.

Some fascinating data have emerged from Bob Motzer's studies of sunitinib. The patients with minimal symptoms and low tumor burden experienced a long survival whether they received sunitinib or interferon (Motzer 2008, 2009). These data indicate something that we don't understand about the disease — that a subset of patients with indolent, slow-growing tumors may simply be observed for a while, but we're not sure how to identify such patients.

To whom should you offer treatment initially? Whom should you observe for six to 12 months before you start treatment? An example would be a 60-year-old patient with asymptomatic, small-volume pulmonary disease. Such a patient you may choose to observe for a while before initiating therapy, especially considering the side-effect profiles of the agents we're using.

DR LOVE: Toni, do you use this strategy?

DR CHOUEIRI: Absolutely. I cannot provide you with an overall percent, but in general I use this approach for patients with a small tumor burden and good Memorial Sloan-Kettering Cancer Center (MSKCC) risk criteria who are reliable for follow-up. I believe that these patients don't necessarily need to begin therapy immediately.

ROLE OF NEPHRECTOMY FOR PATIENTS WITH SYNCHRONOUS mRCC AND PRIMARY RCC

DR LOVE: Dan, what is your approach for a patient presenting with an asymptomatic primary tumor but significant symptomatology from metastatic disease? Where are we right now in terms of nephrectomy for such patients?

DR GEORGE: In general, I almost always treat the symptomatic metastases first. However, you need to individualize. With a newly diagnosed patient, you do not know the natural history of the disease. If you perform a nephrectomy, a few weeks if not a month or more are necessary before you can begin systemic treatment. I'd be concerned particularly with bone metastases. Approximately 30 percent of patients with kidney cancer will develop bone metastases, which tend to be lytic.

DR LOVE: Ron, in what situations, if any, would you not perform a nephrectomy?

DR BUKOWSKI: In some circumstances it is clear that you don't need

to perform an up-front nephrectomy, such as for a patient with highly symptomatic metastatic disease and comorbid features that won't permit it. But nephrectomy is much different from what it was 10 years ago.

It can be performed laparoscopically, which is a simple procedure, and this can even be done with large tumors.

We can administer radiation therapy within a matter of days after surgery, so I'm not sure that we should entirely change the paradigm. I believe that we must study the patient, understand the location of the metastatic disease, know the volume of disease and then try to obtain a sense of how best to treat.

You'll reach the point of having to remove the primary tumor if you're going to provide the patient with any kind of long-term survival.

These tumors don't simply go away. Approximately one third of patients will experience a decrease in tumor size with targeted therapy, but it's less common than we would like. A French trial is evaluating this question, and we hope that trial will provide an answer (1.1).

DR MOTZER: The practice in renal cell cancer in the past was to remove the kidney, and then two studies reported a survival benefit with cytokine therapy and nephrectomy (Flanigan 2001; Mickisch 2001). So the track record exists in kidney cancer, and I believe it will carry over into the targeted therapies.

Having the primary kidney tumor in place can be problematic. Bleeding and other complications can occur. I've had patients who are receiving sunitinib and have problems with hematuria and clotting, and I don't know how much of it is related to the targeted therapy or the disease.

Also, we're not curing the disease, so ultimately, if the patients experience disease progression, the kidney could be a source of morbidity and pain.

1.1

Ongoing and Planned Phase III Studies Integrating Nephrectomy and Sunitinib (S) for the First-Line Management of mRCC

Protocol	No. of patients	Eligibility	Randomization	Primary endpoint	Expected completion
CARMENA[1]	576	Nephrectomy-eligible, clear cell mRCC	Arm 1: Nephrectomy → S Arm 2: S	Overall survival: Equivalence	Dec. 2015
EORTC-33073[2]	440	Clear cell mRCC	Arm 1: Nephrectomy → S Arm 2: S → nephrectomy	Progression-free survival: Superiority	Not reported

Key fundamental questions addressed:
[1] Is cytoreductive nephrectomy clinically beneficial in the treatment of mRCC with TKIs?
[2] If nephrectomy is essential, which intervention (surgical versus TKI therapy) should be performed first?

www.clinicaltrials.gov; Belmunt J. *Ann Oncol* 2009;20(Suppl 1):i13-7; Biwas S et al. *Oncologist* 2009;14(1):52-9.

FIRST- AND SECOND-LINE THERAPY AND SEQUENCING STRATEGIES FOR mRCC

DR LOVE: Bob, what is your algorithm for the first-line treatment of mRCC?

DR MOTZER: I assess the patient's risk according to the MSKCC criteria (Motzer 2002; [1.2]). For patients with favorable or intermediate features, my first choice is sunitinib, considering the responses and outcomes reported with this agent (Motzer 2009). For

1.2 Memorial Sloan-Kettering Criteria for Prognosis of RCC

Risk factors for short survival

- Karnofsky performance status: <80%
- LDH: >1.5 times upper limit of normal
- Hemoglobin: <lower limit of normal
- Corrected serum calcium: >10 mg/dL
- Time from initial diagnosis to treatment with interferon: <1 year

Risk group	Number of risk factors
Poor risk	≥3 risk factors
Intermediate risk	1 to 2 risk factors
Favorable risk	0 risk factors

Motzer RJ et al. *J Clin Oncol* 2002;20(1):289-96.

1.3 Systemic Therapy Guidelines for First-Line and Subsequent Therapy of Advanced Clear Cell Renal Cell Carcinoma

NCCN category	First-line therapy	Patients
1	Sunitinib, pazopanib, bevacizumab/IFN Temsirolimus	— Poor risk
2A	High-dose IL-2, sorafenib	Select patients
2B	Temsirolimus	Select patients of other risk
	Subsequent therapy	
1	Everolimus Sorafenib, sunitinib or pazopanib	Prior TKI Prior cytokine therapy
2A	Sorafenib, sunitinib Temsirolimus	Prior TKI Prior cytokine therapy
2B	Temsirolimus Bevacizumab, IFN or IL-2	Prior TKI —
3	Pazopanib	Prior TKI

Note: Clinical trial participation or best supportive care is also an option.

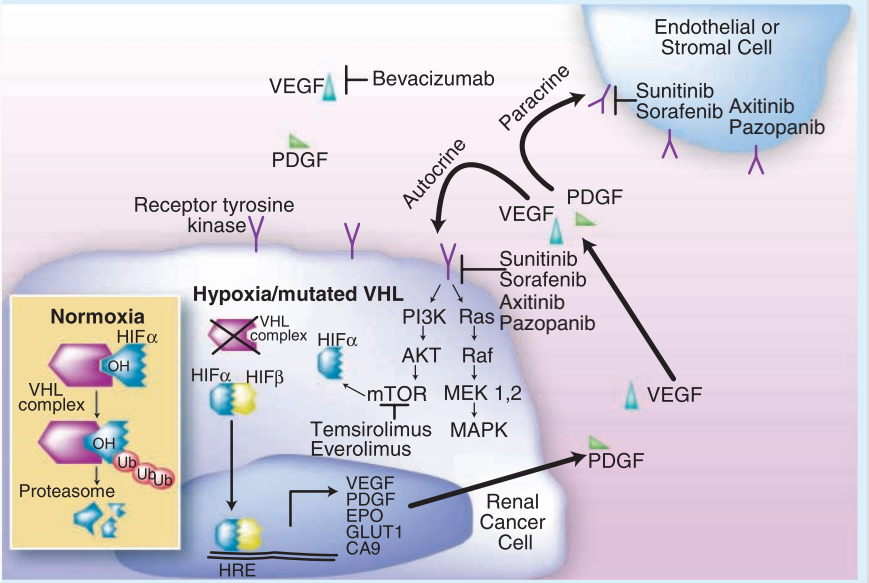
NCCN Categories of Evidence and Consensus

1: High-level evidence, uniform NCCN consensus
2A: Lower-level evidence, uniform NCCN consensus
2B: Lower-level evidence, nonuniform NCCN consensus
3: Any level of evidence, major NCCN disagreement

NCCN Practice Guidelines in Oncology, Kidney Cancer, v.2.2010.

1.4

Key Molecular Pathways in RCC Treatment



In the absence of VHL (or during hypoxic conditions), HIFα accumulates and binds with HIFβ. The HIF complex translocates to the nucleus and binds to HIF-responsive element (*HRE*) enhancer sequence, leading to transcription of hypoxia-induced genes, including VEGF-A and PDGF.

These growth factors are secreted into the extracellular space and can either (*a*) via paracrine action, bind to RTKs located on stromal or endothelial cells, leading to stromal proliferation and angiogenesis or (*b*) via autocrine action, bind to RTKs located on tumor cells, leading to proliferation and survival. Similarly, mTOR is stimulated by a phosphorylation cascade, which involves proteins, including phosphatidylinositol 3-kinase (*PI3K*) and AKT. Once stimulated, mTOR controls protein translation of elements involved in cell cycle progression; in addition, mTOR also controls protein synthesis of HIF-1α in RCC cells.

The signal pathways in RCC can be inhibited at several steps: inhibition of VEGF; inhibition of tyrosine kinase activity of RTK; and inhibition of mTOR.

With permission from AACR. Patel PH et al. **Targeting von Hippel-Lindau pathway in renal cell carcinoma.** *Clin Cancer Res* 2006;12(24):7215-20.

patients with poor-risk features, my choice is either sunitinib or temsirolimus.

The best candidates for temsirolimus are patients who are quite ill from the disease. They experience symptoms such as fatigue, nausea and vomiting and may not be able to tolerate oral therapy.

DR CHOUEIRI: My approach is similar. When I see a patient considered to be at poor risk by MSKCC criteria, I offer temsirolimus. In some situations I administer sunitinib,

however. Some patients do not want to make a weekly trip to the institution for IV temsirolimus therapy and opt for oral sunitinib. For a patient with a large disease burden, regardless of risk criteria, I administer sunitinib if the patient is in need of therapy and by achieving significant tumor shrinkage will achieve considerable palliation.

DR LOVE: Where does everolimus fit into the treatment algorithm?

DR BUKOWSKI: For patients with good- to intermediate-risk disease whose disease has progressed on a VEGF TKI — either sunitinib or sorafenib — the oral mTOR inhibitor everolimus has Level 1 evidence to support it as the standard second-line therapy.

DR LOVE: Bob, where do you think we will be in two or three years? Are a lot of newer agents becoming available, or have we hit a plateau in renal cell cancer?

DR MOTZER: For the most part, the agents that seem to have activity are VEGF directed — either against the ligand or against the receptor — or the mTOR class of agents (1.4). A couple of different drugs are on the horizon that have slightly different profiles and may be more selective and better tolerated, but we need to look for new targets while we fine tune the best first-line treatment and the optimal sequence of therapies. ■

SELECT PUBLICATIONS

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Mickisch GH et al. **Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial.** *Lancet* 2001;358(9286):966-70.

Motzer RJ et al. **Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2009;27(22):3584-90.

Motzer RJ et al. **Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma.** *Cancer* 2008;113(7):1552-8.

MANAGEMENT OF SIDE EFFECTS FROM VEGF MONOCLONAL ANTIBODIES, TYROSINE KINASE INHIBITORS (TKIs) AND mTOR INHIBITORS

MANAGEMENT OF VEGF TKI SIDE EFFECTS

DR LOVE: Toni, would you discuss the safety and tolerability profiles of the different first-generation VEGF TKIs?

DR CHOUEIRI: Fatigue and diarrhea are significant issues with sunitinib, but we also see bone marrow suppression in eight to 10 percent of patients and Grade III/IV neutropenia and thrombocytopenia.

Patients receiving sorafenib have more hand-foot skin reactions, but the fatigue seems to be less of a problem.

DR LOVE: Bob, what about sunitinib-associated hypertension?

DR MOTZER: Typically, the patient's blood pressure is high during the four weeks on and then it decreases during the two weeks off.

We have the patients measure their blood pressure at home, and we initiate antihypertensive agents. Often they have to learn how to change the dose of their antihypertensive agent during the two weeks off of sunitinib.

The antihypertensive agent we use commonly is amlodipine besylate because it doesn't interact with sunitinib. Patients may be receiving 10 mg of amlodipine besylate during the first 28 days, and at two weeks off they take five mg.

That's been one of the challenges with the intermittent schedule of sunitinib. Patients' blood pressure levels can drop quite low during the two weeks off if you don't modify the antihypertensive agents.

DR LOVE: Ron, what are your thoughts on the use of alternative sunitinib dose schedules and/or reductions for patients with metastatic RCC (2.1)?

DR BUKOWSKI: I begin with 50 mg administered for four weeks out of six, and fatigue is generally what drives my decision to decrease the dose to 37.5 mg. The last two weeks of the initial 50-mg dose are the worst. We attempt to minimize symptoms for these patients but recognize that fatigue interferes with their daily activities. At some point around three to five months, they need a dose reduction or a break of a week or two longer.

DR MOTZER: I would reduce the dose to 25 mg four weeks on, two weeks off. If the patient didn't tolerate that, I would stop the treatment and either observe or switch to something different. If patients don't tolerate sunitinib, I often switch to sorafenib.

DR GEORGE: When you consider this four-two regimen, it seems arbitrary.

2.1

Sunitinib: Treatment and Dose Adjustments in the Treatment of Metastatic Renal Cell Carcinoma (RCC)

"The recommended dose for sunitinib for patients with advanced RCC is one 50-mg oral dose daily, with or without food, on schedule 4/2. Most side effects are reversible and should not result in discontinuation of sunitinib. If necessary, toxicities may be managed through dose adjustments or interruptions.

A standard dose modification in 12.5-mg steps is recommended based on individual safety and tolerability: dose level 1, 50 mg for 4 weeks, 2 weeks off; dose level 2, 37.5 mg for 4 weeks, 2 weeks off; dose level 3, 25 mg for 4 weeks, 2 weeks off. Tumors tend to regrow during the 2-week break period or if plasma concentrations are too low for complete receptor inhibition.

Discontinuation of sunitinib is indicated in the presence of clinical evidence of congestive heart failure and in patients with symptoms of pancreatitis or hepatic failure."

[Citations omitted]

Hutson TE et al. *Oncologist* 2008;13(10):1084-96.

When sunitinib was initially under development, a number of different regimens were evaluated in Phase I testing, including a two-one regimen.

However, other dosing regimens are effective. Having said that, I don't like to mess with success. If I'm forced by limiting toxicity to decrease the dose well below 37.5 mg at week three or four, that's when I start to contemplate other approaches.

DR LOVE: Ron, what are your thoughts on the VEGF TKIs and the correlation between dose and benefit?

DR BUKOWSKI: All the data thus far have come from retrospective analyses correlating the area under the plasma concentration-time curve (AUC) with response (Houk 2009).

We don't have any prospective evaluation of a dose and schedule. That's forthcoming, and I hope we receive data on the comparison of sunitinib 37.5 mg versus 50 mg at ASCO this year.

DR CHOUEIRI: The study by Houk and colleagues evaluating sunitinib dose in the blood and measuring the AUC of sunitinib reported that patients with high or above-median AUC had better responses, progression-free survival and overall survival (Houk 2009; [2.2]). This is why in my practice I try as much as possible to keep the dose high, knowing that in many situations I'm not able to do so.

DR LOVE: Toni, what about dose-escalated sorafenib for patients with metastatic RCC?

DR CHOUEIRI: Recent data from Dr Amato on sorafenib dose escalation from 400 mg BID to 600 mg BID a month to 800 mg BID as tolerated showed that the majority of patients — approximately 90 percent — were able to tolerate the increase.

The response rate reached 55 percent (Amato 2008). The response rate with single-agent sorafenib at the FDA-recommended dose is two to 10 percent.

I haven't seen that in my practice. I haven't been able to escalate the sorafenib dose except for patients who have already received sorafenib for a long time. If they experience disease progression, I increase the dose to 600 mg BID and repeat the CT scan.

I haven't started with 800 mg BID directly. So the result reported by Dr Amato seems to be an outlier in our medical experience overall.

2.2

Probability of Partial or Complete Response Based on Mean Daily Sunitinib Exposure among Patients with Metastatic RCC

"The results of this meta-analysis indicate that increased exposure to sunitinib is associated with improved clinical outcomes (longer TTP, longer OS, greater chance of antitumor response), as well as some increased risk of adverse events. A sunitinib 50-mg starting dose seems reasonable, providing clinical benefit with acceptably low risk of adverse events."

Houk BE et al. *Cancer Chemother Pharmacol* 2009;[Epub ahead of print].

TOLERABILITY AND SIDE EFFECTS OF BEVACIZUMAB (WITH OR WITHOUT INTERFERON)

DR LOVE: Bob, what is known about dose reduction of interferon when administered in combination with bevacizumab and the effect on efficacy?

DR MOTZER: Data presented by Bernard Escudier from the AVOREN trial, which evaluated bevacizumab with interferon for patients with metastatic RCC, indicated that if you start the combination but need to reduce the interferon dose, this doesn't appear to negatively affect the efficacy. Those patients had the same favorable outcomes as patients who continued on the combination (Melichar 2008; [2.3]).

DR CHOUEIRI: It's unfortunate that bevacizumab was the first agent to be investigated and to yield a positive result in a randomized Phase II trial for patients who failed on interleukin-2 (Yang 2003), and only recently — more than five years later — bevacizumab/interferon received approval.

DR LOVE: It's amazing when you consider that only five years ago we had limited treatment options, such as single-agent interferon, and now everything has changed.

DR GEORGE: It's interesting in considering the new approval for the bevacizumab/interferon combination. We have a lot of bad memories, yet a subset of patients respond to interferon, and you can titrate to toxicity as we do with the new targeted therapies.

DR LOVE: Ron, are additional data available with single-agent bevacizumab?

2.3

AVOREN: Subgroup Analysis of Reduced-Dose versus Full-Dose Interferon (IFN) in Combination with Bevacizumab (Bev) in Previously Untreated mRCC

Parameter	Reduced-dose IFN		Full-dose IFN		Total population	
	Bev + IFN (n = 124[a])	IFN + placebo (n = 90[a])	Bev + IFN (n = 174[a])	IFN + placebo (n = 186[a])	Bev + IFN (n = 298[a])	IFN + placebo (n = 276[a])
12-month PFS rate*	0.524		0.361		0.427	
Median duration of PFS*	HR = 0.63, $p = 0.0026$		HR = 0.69, $p = 0.0007$		HR = 0.63, $p < 0.0001$	
Overall response	34%	17% $p = 0.0181$	31%	12% $p < 0.0001$	32%	13% $p < 0.0001$
Median duration of response[b]	13.6 mo	8.3 mo	13.5 mo	14.0 mo	13.5 mo	11.1 mo

[a] Patients assessable; [b] Patients with measurable disease at baseline
* Values < 1.0 favor bevacizumab-containing regimens
PFS = progression-free survival; HR = hazard ratio

Melichar B et al. *Ann Oncol* 2008;19(8):1470-6.

DR BUKOWSKI: We're in the era now of Level 1 evidence for this disease, and unfortunately the Level 1 evidence lies with bevacizumab and interferon (Escudier 2007; Melichar 2008).

Do we surmise that bevacizumab alone would have an effect? Yes, without a doubt. It's unfortunate that we don't have the data. The closest example is from the cooperative group four-arm study, in which bevacizumab alone is a single arm (3.6).

Unfortunately, the study population is not all patients with untreated disease, but it will provide us with another data set to evaluate and judge for ourselves.

MANAGEMENT OF COMPLICATIONS FROM mTOR INHIBITORS

DR LOVE: Toni, one of our recent Patterns of Care surveys asked investigators and community oncologists about the side effects and complications associated with mTOR inhibitors, and only 60 percent of oncologists were aware of the hyperglycemia and hyperlipidemia.

Only 39 percent were aware of noninfectious pneumonitis (2.4). Would you discuss what we know about the complications and side effects of these agents and how you monitor them?

DR CHOUEIRI: The two mTOR inhibitors currently approved for metastatic RCC — temsirolimus and everolimus — are both sirolimus analogs. Side effects include fatigue, nausea, some gastrointestinal disturbances, mucositis and mouth sores.

The side effects and lab abnormalities that could become problematic are distinct, including hyperlipidemia, hypercholesterolemia and hypertriglyceridemia. I check my patients at baseline and sometimes with every other cycle. Hyperglycemia can become problematic, especially for patients with uncontrolled diabetes.

Another problematic side effect that can occur with both temsirolimus

2.4

National Patterns of Care Study with Clinical Investigators (N = 12) and Practicing Oncologists (N = 100)

Which of the following is associated with the use of the mTOR inhibitors temsirolimus and everolimus?

	Clinical investigator	Practicing oncologist
Hyperglycemia	100%	60%
Hypercholesterolemia	100%	56%
Noninfective pulmonary pneumonitis	**100%**	**39%**
Increased susceptibility to infections	92%	37%
Hypersensitivity reactions	67%	39%
Neutropenia	50%	34%
Stomatitis	83%	27%
Renal failure	67%	21%

Research To Practice Patterns of Care Study, July 2009.

and everolimus is noninfectious pneumonitis. It's an inflammation in the lungs that is mainly detected on chest x-rays or CT and can become symptomatic with shortness of breath and fever.

This phenomenon has been evaluated more specifically with everolimus in Dr Motzer's RECORD-1 trial, in which the overall incidence of noninfectious pneumonitis was approximately 15 percent (Kay 2009).

If you see some infiltration on CT scans and the patient is not experiencing symptoms, you continue the drug. However, if you have severe infiltration with shortness of breath and fever, then you should discontinue the drug.

I follow patients on these drugs carefully. I see them more frequently in the clinic. I may not wait another eight or 10 weeks for follow-up CT scans — I may repeat them every two weeks, and I ask patients to call often. These side effects must be recognized. Most of the time, the pneumonitis is reversible.

Sometimes, if it's severe and symptomatic, you need to administer steroids. Some guidelines are under development, but most of us reduce the dose of everolimus from 10 mg to five mg.

DR MOTZER: We follow lipid profiles also. Patients commonly develop elevated triglycerides. Often if they have predisposing factors or are receiving statins, this is worse. For the most part, however, it responds well to statin therapy and is not problematic.

As far as the hyperglycemia goes, we see mild elevations in sugar, but the patients who could run into trouble are those who have diabetes at the start. They experience acute elevations of their glucose levels.

In my experience with temsirolimus, some patients have even required hospitalization for glucose management. ■

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Escudier B et al. **Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomized, double-blind phase III trial.** *Lancet* 2007;370(9605):2103-11.

Houk BE et al. **Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: Results of a pharmacokinetic/pharmacodynamic meta-analysis.** *Cancer Chemother Pharmacol* 2009;[Epub ahead of print].

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NOVEL MULTIKINASE VEGF TKIs: PAZOPANIB AND AXITINIB

DR LOVE: What do we know about other VEGF TKIs such as pazopanib and axitinib and how these compare to sunitinib and sorafenib?

DR GEORGE: The data are from indirect comparisons across studies. From the efficacy data that we have for pazopanib (3.2), I believe that it is comparable in efficacy to sunitinib across the board. I view axitinib as potentially being a more potent inhibitor as a single drug. It is being developed as a second-line drug that could work after treatment with an initial TKI like sunitinib.

DR CHOUEIRI: A Phase III trial is currently accruing that will compare sunitinib to pazopanib (NCT00720941) head to head (3.5). From what we do know about pazopanib in terms of toxicity, it appears that less fatigue, bone marrow suppression, rash and mucositis occur with pazopanib. However, it seems that Grade III and IV LFT abnormalities are higher (3.3, 3.4).

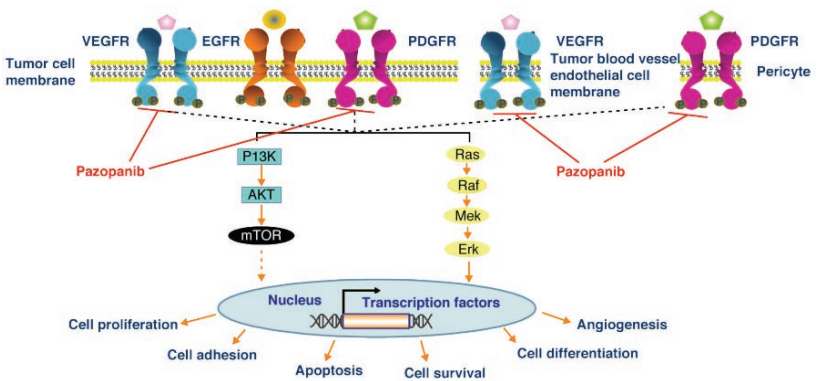
DR BUKOWSKI: The hepatic toxicity is in the form of transaminitis. It is reversible, and one of the recommendations for this agent as a result is careful monitoring of transaminase levels.

DR GEORGE: From my experience with pazopanib, another side effect is hair whitening or streaking. This occurs in approximately 20 percent of patients and is believed to result from C-kit inhibition (Moss 2003).

DR BUKOWSKI: Axitinib perhaps brings a higher incidence of hand-foot symptoms, more gastrointestinal disturbances and more hypertension.

3.1

Pazopanib: Mechanisms of Action



With permission from Sonpavde G et al. *Expert Opin Investig Drugs* 2008;17(2):253-61.

3.2 Efficacy of Oral Pazopanib in Patients with Advanced RCC

Final efficacy analysis	Phase II trial[1] (n = 225)	Phase III open-label study[2] (n = 290)
Response rate (CR + PR)	34.7%	30%
Stable disease	44.9%	38%
Progression-free survival	12 months	9.2 months

CR = complete response; PR = partial response

[1] Hutson TE et al. *J Clin Oncol* 2010;28(3):475-80; [2] Sternberg CN et al. *J Clin Oncol* 2010;28(6):1061-8.

3.3 Select Adverse Events Reported with Pazopanib and Axitinib in Patients with mRCC

Adverse event	Pazopanib[1] (n = 225)		Axitinib[2] (n = 52)	
	Any grade	Grade III/IV	Any grade	Grade III/IV
Hypertension	41%	9%	58%	15%
Diarrhea	63%	4%	60%	10%
Fatigue	46%	5%	52%	8%
Hair depigmentation	43%	0%	—	—
Hoarseness	—	—	37%	0%
ALT increase	14%	<6%	—	—
AST increase	12%	<4%	—	—

[1] Hutson TE et al. *J Clin Oncol* 2010;28(3):475-80; [2] Rixe O et al. *Lancet Oncol* 2007;8(11):975-84.

3.4 Dr Thomas Hutson's Perspective on the Potential Tolerability Advantages with Newer-Generation VEGF TKIs in Renal Cell Carcinoma

"Our hope is that the newer second- or third-generation VEGF TKIs will have less off target inhibition and improved efficacy and safety profiles, which will make them more amenable to long-term use. Cora Sternberg reported phase III data from ASCO with pazopanib, which demonstrated a response rate and progression-free survival that was very similar to sunitinib but with a somewhat different toxicity profile.

In particular, less fatigue, hand-foot syndrome, mucositis and cytopenias were observed. So, it appears to have potentially less of the chronic toxicities that impact the ability of patients to tolerate longer-term use of sunitinib."

Research To Practice. *Renal Cell Cancer Update* Special Edition: Therapeutic Strategies in the Management of Advanced Renal Cell Carcinoma 2009.

3.5

Phase III Trial Comparing Pazopanib to Sunitinib

Protocol IDs: COMPARZ, 108844, NCT00720941
Target Accrual: 876 (Open)

Study Contact
GSK Clinical Trials Call Center
Tel: 877-379-3718

Eligibility

- Previously untreated, locally advanced and/or metastatic RCC

NCI Physician Data Query, October 2009; **www.clinicaltrials.gov**, October 2009.

COMBINATIONS OF BIOLOGIC AGENTS

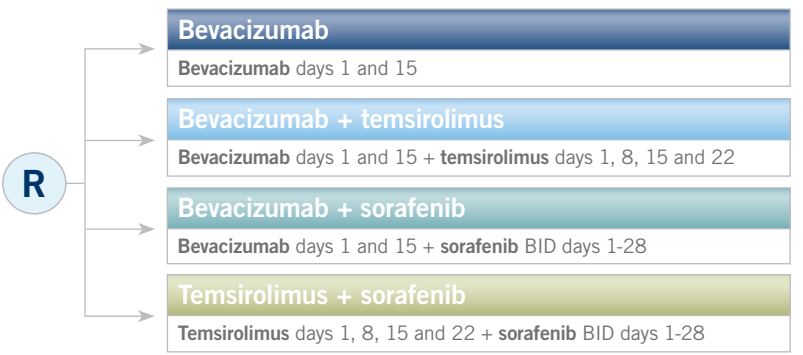
DR LOVE: Dan, where are we now with investigations of combination targeted therapy in advanced RCC?

DR GEORGE: A four-arm Intergroup study is evaluating three doublets and an arm of bevacizumab alone (3.6). The three doublets are bevacizumab/temsirolimus at full dose, temsirolimus/sorafenib and bevacizumab/sorafenib at reduced doses to make them tolerable.

3.6

Phase II Randomized Trial of Bevacizumab, Sorafenib and Temsirolimus (BeST) for Patients with Metastatic Clear Cell RCC

Protocol ID: ECOG-E2804; **Target Accrual:** 360



Eligibility

- No history or clinical evidence of CNS disease, including primary brain tumor or brain metastases
- No history of bleeding diathesis or coagulopathy
- No clinically significant cardiovascular disease
- No serious, nonhealing wound, ulcer or bone fracture

www.clinicaltrials.gov. Accessed March 2010.

DR BUKOWSKI: Combination work is important, and we've been tinkering with combinations of targeted agents in renal cancer ever since the possibility arose of combining sorafenib with bevacizumab. We have combined bevacizumab with most drugs.

The hope with combination therapy is that we will see a maximizing of benefit or an increase in response rate. We haven't seen any Level 1 evidence demonstrating that a combination is better than other therapy, with the exception of the bevacizumab/interferon combination that had a clear effect on progression-free survival (Escudier 2007).

The side effects are greater with combination therapy, which is exemplified by the serious toxicities observed in Bob's study with sunitinib and bevacizumab (Feldman 2009; [3.7]).

DR LOVE: Bob, would you elaborate on your experience with combining biologic agents?

DR MOTZER: In my experience with TKIs, it is possible to treat with a combination but it isn't tolerated for long and you need to reduce the dose.

I believe it is possible to obtain a greater long-term benefit and better safety for patients through the sequential use of agents instead of with concurrent use.

That said, the combinations of bevacizumab with everolimus and bevacizumab with temsirolimus have been reported to be safe at full doses.

These two combinations are currently being evaluated in randomized trials. ■

3.7

Grade III or Higher Adverse Events and Laboratory Toxicities: A Phase I Trial of Bevacizumab (Bev) with Escalating Doses of Sunitinib for Patients with Metastatic Renal Cell Carcinoma

Event or toxicity	Cohort 1 (n = 7) Bev + sunitinib 25 mg	Cohort 2 (n = 6) Bev + sunitinib 37.5 mg	Cohort 3 (n = 12) Bev + sunitinib 50 mg
Hypertension	29%	50%	83%
Proteinuria	43%	0%	50%
Thrombocytopenia	0%	0%	50%
Hand-foot skin reaction	29%	33%	0%
Fatigue	14%	17%	8%

Feldman DR et al. *J Clin Oncol* 2009;27(9):1432-9.

SELECT PUBLICATIONS

Escudier B et al. **Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomized, double-blind phase III trial.** *Lancet* 2007;370(9605):2103-11.

Feldman DR et al. **Phase I trial of bevacizumab plus escalated doses of sunitinib in patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2009;27(9):1432-9.

Hutson TE et al. **Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2010;28(3):475-80.

Moss K et al. **Hair depigmentation is a biological readout for pharmacological inhibition of KIT in mice and humans.** *J Pharmacol Exp Ther* 2003;307:476-80.

ADJUVANT THERAPY FOR EARLY RCC

DR LOVE: In our recent Patterns of Care study, none of the clinical investigators surveyed use adjuvant therapy off study, but 29 percent of the community oncologists do. What is your approach?

DR MOTZER: I practice evidence-based medicine, and the role for adjuvant therapy is not established.

DR CHOUEIRI: I haven't done so outside of clinical trials with good reason.

We don't have evidence to support the off-protocol use of adjuvant therapy, and I've seen no hint that adjuvant therapy matters. We also don't know for how long to administer it.

DR BUKOWSKI: I wouldn't either. However, in Japan they administer interferon after the removal of metastatic disease, and they maintain that their results are far superior to ours in that setting.

DR CHOUEIRI: Randomized trials have examined adjuvant therapy in RCC using chemotherapy, radiation therapy, interferon, interleukin-2 and different vaccines.

None have yielded results indicating that the tested adjuvant therapy should become standard. Several large adjuvant trials are ongoing worldwide, including the large Intergroup ASSURE trial led by ECOG, in which patients are randomly assigned to one year of sorafenib, sunitinib or placebo (4.1). ■

4.1

Ongoing Phase III Clinical Trials of Adjuvant Tyrosine Kinase Inhibitor Therapy for RCC

Trial identifier	Estimated enrollment (N)	Select eligibility	Treatment arms
ASSURE (NCT00326898)	1,923	• Intermediate- or high-risk disease • No evidence of residual or metastatic disease	Sorafenib vs sunitinib vs placebo
S-TRAC (NCT00375674)	500	• High-risk renal cancer • Predominant clear cell histology • No evidence of macroscopic disease after surgery	Sunitinib vs placebo
SORCE (NCT00492258)	1,656	• Intermediate- or high-risk disease • No residual/metastatic disease	Sorafenib vs placebo

www.clinicaltrials.gov. Accessed March 2010.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **To evaluate the role of cytoreductive nephrectomy for patients who present with metastatic renal cell carcinoma (mRCC), the CARMENA trial randomly assigns patients to _____ alone or after nephrectomy.**
   a. Sorafenib
   b. Sunitinib
   c. Temsirolimus

2. **In a study by Wood and colleagues evaluating sunitinib for patients with unresectable primary RCC, approximately what proportion of the tumors were converted to resectable disease?**
   a. 10 percent
   b. 20 percent
   c. 40 percent

3. **A large Phase III trial of sunitinib versus interferon-α for patients with previously untreated mRCC demonstrated significant improvement in _____ among patients who received sunitinib.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b

4. **Houk and colleagues published pharmacokinetic/pharmacodynamic data on sunitinib for the treatment of mRCC showing that total drug AUC correlated significantly with which of the following?**
   a. Probability of response
   b. Time to disease progression
   c. Overall survival
   d. All of the above

5. **The recommended standard starting dose of sunitinib for patients with advanced RCC is _____ daily, with or without food, on a four-weeks-on, two-weeks-off schedule.**
   a. 25 mg
   b. 37.5 mg
   c. 50 mg

6. **According to a subset analysis of the AVOREN trial, patients who received reduced doses of interferon in combination with bevacizumab had _____ efficacy outcomes compared to those who received full doses of interferon in combination with bevacizumab.**
   a. Better
   b. Worse
   c. Similar

7. **Which of the following metabolic abnormalities may be associated with the mTOR inhibitors?**
   a. Hyperglycemia
   b. Hypercholesterolemia
   c. Hypertriglyceridemia
   d. All of the above

8. **Noninfectious pneumonitis, a potentially serious adverse event, has been reported in association with _____ therapy.**
   a. mTOR inhibitor
   b. VEGF tyrosine kinase inhibitor
   c. VEGF monoclonal antibody

9. **The ongoing Phase II BeST trial is comparing _____ alone to three different treatment doublets for patients with clear cell mRCC.**
   a. Sorafenib
   b. Sunitinib
   c. Bevacizumab
   d. Interferon

10. **An ongoing Phase III trial is evaluating the efficacy and safety of pazopanib versus sunitinib as first-line therapy for patients with locally advanced or metastatic RCC.**
    a. True
    b. False

Post-test answer key: 1b, 2c, 3c, 4d, 5c, 6c, 7d, 8a, 9c, 10a

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Renal Cell Cancer Update Special Edition — 2010

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Role of cytoreductive nephrectomy for mRCC in the era of effective targeted therapies	4 3 2 1	4 3 2 1
Watchful waiting for patients with asymptomatic mRCC	4 3 2 1	4 3 2 1
Dose reduction, schedule change or alternative therapy for patients intolerant to sunitinib	4 3 2 1	4 3 2 1
Activity and side effects of the novel VEGF TKIs pazopanib and axitinib	4 3 2 1	4 3 2 1
Distinct side effects of mTOR inhibitors: hyperglycemia, hyperlipidemia and noninfectious pneumonitis	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Identify patient characteristics that may help to distinguish the individualized utility of cytoreductive nephrectomy in the era of effective targeted therapies for metastatic renal cell carcinoma (mRCC). . . . . 4 3 2 1 N/M N/A
- Apply the results of existing and emerging clinical research to the evidence-based selection of front-line and subsequent therapy for mRCC.. . . . . 4 3 2 1 N/M N/A
- Develop an approach for the sequencing of therapies for advanced RCC, incorporating biologic response modifiers, tyrosine kinase inhibitors (TKIs), anti-VEGF antibodies and mTOR inhibitors.. . . . . 4 3 2 1 N/M N/A
- Educate patients with mRCC about the safety and tolerability of multikinase VEGF TKIs, mTOR inhibitors and VEGF monoclonal antibody therapy.. . . . . 4 3 2 1 N/M N/A
- Recommend supportive measures to enhance the tolerability of targeted therapeutic agents for RCC, including the use of dose reductions, schedule changes or alternative therapies. . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for and early efficacy of novel investigational compounds demonstrating activity in RCC. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with RCC about the availability of ongoing clinical trial participation. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Ronald M Bukowski, MD	4 3 2 1	4 3 2 1
Toni K Choueiri, MD	4 3 2 1	4 3 2 1
Daniel J George, MD	4 3 2 1	4 3 2 1
Robert J Motzer, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: DrNeilLove@ResearchToPractice.com
For CME/CNE Information	Email: CE@ResearchToPractice.com

Renal Cell Cancer™

U P D A T E

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