Clinical Treatment Decisions for Advanced Renal Cell Cancer

Presented by Toni K. Choueiri, MD

Abstract

Seven targeted agents have improved the prognosis of advanced renal cell carcinoma (RCC), but none are effective in the post-nephrectomy adjuvant setting. Among the available first-line options for advanced RCC, sunitinib remains the most commonly used first-line therapy, but several studies suggest pazopanib may be better tolerated. Increasingly, choice of therapy may be driven by toxicity profiles. Cytoreductive nephrectomy remains important, even in the era of targeted therapies in selected patients. (*JNCCN* 2013;11:694–697)

For the treatment of advanced renal cell cancer (RCC), 7 targeted agents have been approved in less than 8 years, which has greatly extended progression-free survival (PFS; Table 1). As even more targeted agents emerge from the pipeline, the choice among them will be based on efficacy, access, toxicity profile, physician preference, and, increasingly, cost, said Toni K. Choueiri, MD, head of the Kidney Cancer Center at Dana-Farber Cancer Institute.

Because RCC is an angiogenically rich tumor, targeting the vascular endothelial growth factor (VEGF) receptor is a rational treatment approach. Upstream of VEGF, the mTOR pathway is important in cell metabolism and proliferation. The anti-VEGF tyrosine kinase inhibitors (TKIs) and mTOR inhibitors, therefore, have become useful classes of agents and may be used based on line of therapy and risk factors. Several large, well-powered phase III studies showed significant activity), demonstrating proof of principle, which is that targeting VEGF acts on the disease biology and slows the progression of disease, Dr. Choueiri said.

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Dr. Choueiri has disclosed that he serves as a consultant for GlaxoSmithKline; Novartis Pharmaceuticals Corporation; AVEO Pharmaceuticals, Inc.; and Pfizer Inc.

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Cytoreduction Nephrectomy in the Targeted Therapy Era

The need to obtain tumor tissue in the era of targeted therapies renders biopsy and/or cytoreductive nephrectomy still relevant, according to Dr. Choueiri. He led a systematic review that confirmed an overall survival (OS) advantage for patients who received nephrectomy as a component of contemporary treatment, though patient selection is important, he said.[1]

The NCCN Panel recommends nephrectomy for patients with limited disease burden, good performance status, absence of brain metastases and, for palliation, hematuria or other symptoms related to the primary tumor. The French CARMENA study should further inform on this question by evaluating outcomes after nephrectomy plus sunitinib versus sunitinib alone.

Prognosis

Risk factors associated with prognosis irrespective of type of treatment include time from diagnosis to treatment, hemoglobin, calcium, performance status, neutrophil count, and platelet count.

In the cytokine era, patients with 3 or more risk factors lived an average of about 5 months, and patients without risk factors lived about 30 months. In the era of targeted therapies, prognosis still depends on risk factor

Table 1 Seven Targeted Agents for Advanced RCC as of March 2013

Agent	Target	Efficacy in Randomized Phase III Trials			
		Comparison	No.	ORR	PFS, (mo)
Bevacizumab	VEGF	IFN-α +/- bevacizumab	649	31% vs 13%	10.2 vs 5.4
		IFN-α +/- bevacizumab	732	26% vs 13%	8.5 vs 5.2
Sunitinib	VEGF receptor	Sunitinib vs IFN-α	732	37% vs 9%	11.1 vs 5
Sorafenib	VEGF receptor	Sorafenib vs placebo[4]	750	10% vs 2%	5.5 vs 2.8
Pazopanib	VEGF receptor	Pazopanib vs placebo	903	30% vs 3%	11.1 vs 2.8/9.2 vs 4.2 (untreated/treated)
Temsirolimus	mTOR	Temsirolimus vs IFN-α vs both agents	435	9% vs 7% vs 11%	3.7 vs 1.9
Everolimus	mTOR	Everolimus vs placebo	626	2% vs 0%	4.9 vs 1.8
Axitinib	VEGF receptor	Axitinib vs sorafenib	416	19% vs 9%	6.7 vs 4.7

These agents are the first new drugs to be approved for renal cell carcinoma (RCC) in almost 2 decades. Three of these 7 agents target the vascular endothelial growth factor (VEGF) pathway, whereas 1 targets the mTOR pathway. All of these agents significantly prolong the time to disease progression in comparison with either placebo or interferon (IFN).[1–5]
Abbreviations: ORR, overall response rate; PFS, progression-free survival.

profile; however, OS times are much longer.[2] For patients with intermediate risk, the most common patient subgroup (60% of all metastatic RCC patients), OS has improved from about 14 months to 28 to 30 months now, he noted.

Variable outcomes according to risk status have been shown consistently.[3,4] In a 2009 study of 645 patients receiving anti-VEGF therapy, median OS for patients with a favorable risk profile was not reached after 24 months of follow-up. It was 27 months in patients with 1 or 2 risk factors and 8.8 months in patients with 3 to 6 risk factors.[3]

Choosing Among Many Treatment Options

For patients with relapsed or stage IV RCC or those whose disease is surgically unresectable, systemic therapy options are plentiful. As first-line options, category 1 evidence exists for sunitinib, pazopanib, bevacizumab plus interferon (though toxicity and the route of use limits the utility of this combination), and temsirolimus for poor-prognosis patients (category 2B for other risk groups). Sorafenib is acceptable for selected patients but is not a preferred agent. High-dose interleukin-2 is also acceptable in some cases. Clinical trials are always encouraged.

"We have an embarrassment of riches," Dr. Choueiri said, but noted that current recommendations are based on studies that evaluated novel agents versus treatments that are no longer the standard of care. "We are beginning to see studies comparing the more effective agents, such as the COMPARZ study."

Differences in Toxicity Can Drive Treatment Choice

The difference in toxicity profiles of the TKIs is emerging as a factor in their utility, he added. Although sunitinib is the most commonly used first-line agent, pazopanib may be better tolerated, 2012 findings suggest. "This is important, because these drugs are taken continuously," he emphasized.

The 2012 COMPARZ trial involving 1110 patients with metastatic disease showed pazopanib to be non-inferior to sunitinib and to be associated with less hand-foot skin reaction, fatigue, stomatitis, and mucositis, though more liver function abnormalities and hair color changes.[5] Median PFS was 8.4 months with pazopanib and 9.5 months with sunitinib, a non-significant difference. These results mirror a smaller patient preference study called PISCES, which showed that 70% of patients preferred pazopanib and 22% preferred sunitinib (P <.001).[6] The innovative study suggests that patient preference is another way to evaluate adverse events and choose treatment, he said. Most side effects with TKIs are manageable and not a reason for discontinuation of

treatment, he added, although serious adverse effects are occasionally seen and should be on the clinician's radar.

Interestingly, the occurrence of hypertension and hand-foot skin reactions with TKIs has been associated with an OS benefit.[7,8] Therefore, some degree of toxicity can be considered positive, he said.

More Front-Line Options Poised for Use

Axitinib, a highly specific VEGF receptor inhibitor approved for second-line treatment, was tested in VEGF-naive advanced RCC, Dr. Choueiri said. In the second-line AXIS trial, axitinib was associated with a 33.5% improvement in PFS versus sorafenib (P <.0001),[9] but in the first-line setting it was numerically though not significantly better than sorafenib (median PFS, 10.1 vs 6.5 months) in a 2013 study that may have been underpowered.[10] Tivozanib is another highly selective TKI that proved superior to sorafenib in an appropriately powered phase III trial presented at ASCO 2012.[11] Median PFS was 11.9 months with tivozanib versus 9.1 months with sorafenib (P = .042), and tolerability was, in general, good.

Second-Line Therapy and Beyond

Level 1 evidence backs second-line treatment with everolimus and axitinib. In the RECORD-1 study, median PFS was 5.49 months with everolimus versus 1.87 months with placebo (P <.001).[12] In the AXIS trial, axitinib was significantly superior to sorafenib, and although the drug only added 2 months of PFS, its activity was robust among patients who experienced progression after cytokine treatment (64% risk reduction; P <.0001).[9] The more common practice, however, is to treat after sunitinib, and axitinib delayed progression in these patients by 1.4 months (P = .011).

The optimal sequencing of axitinib and everolimus as second-line choices is currently unknown, but response to the initial agent could be a way to select treatment. After a durable response to a TKI, axitinib may be a smart choice, while patients with a short PFS interval on a TKI may benefit most from everolimus. Interestingly, several large retrospective studies suggested that the clinical response to a second-line VEGF inhibitor is not dependent on response to the first-line VEGF inhibitor.[13] One large second-line study of temsirolimus versus sorafenib after sunitinib was recently presented (INTORSECT). No PFS benefit was shown between both arms.[14] An intriguing OS benefit was seen with sorafenib over temsirolimus, although OS was a secondary endpoint.

Combinations of targeted agents do not add activity at this stage, only toxicity; therefore, they should not be given outside of a clinical trial, Dr. Choueiri noted. Numerous biomarkers are under investigation, but none should be clinically applied at this time, he said.

Adjuvant Therapy and Other Histologies

In contrast to metastatic RCC, adjuvant treatment provides no demonstrable benefit. Trials with VEGF TKIs and mTOR inhibitors are underway, and patients with high-risk disease are encouraged to enroll or be treated with observation only, the Panel recommended. Clinical trial enrollment is also the preferred approach for patients with RCC of nonclear cell histology, which have not shown a good response to VEGF or mTOR inhibitors.

In conclusion, Dr. Choueiri expressed optimism that "the next 5 years will hold new targets and combinations of agents beyond the VEGF and mTOR inhibitors." He predicted that non-VEGF–mediated angiogenesis targets will be revealed and that their targeting will help prevent tumors' "angiogenic escape." Targets upstream of mTOR, including AKT and PI3K, will also be explored, and novel immunotherapy approaches (such as immune checkpoint blockade) may prove effective. "We still need novel targets to induce durable responses," he said.

References

1. Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. J Urol 2011;185:60–66.
2. Manola J, Royston P, Elson P, et al. Prognostic model for survival in patients with metastatic renal cell carcinoma: results from the international kidney cancer working group. Clin Cancer Res 2011;17:5443–5450.
3. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794–5799.
4. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic

Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141–148.

5. Motzer RJ, Hutson TE, Reeves J, et al: Randomized open-label phase III trial of pazopanib versus sunitinib in first-line treatment of patients with metastatic renal cell carcinoma (MRCC): results of the COMPARZ trial [abstract]. Presented at the 37th Annual ESMO Conference, September 28 to October 3, 2012. Vienna, Austria. Abstract LBA8.
6. Escudier B, Porta C, Bono P, et al: Patient preference between pazopanib and sunitinib: results of a randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma—PISCES study, NCT0106431 [abstract]. J Clin Oncol 2012;30(Suppl 15):Abstract CRA4502.
7. Rini BI, Schiller JH, Fruehauf JP, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. Clin Cancer Res 2011;17:3841–3849.
8. Michaelson MD, Cohen DP, Li S, et al. Hand-foot syndrome as a potential biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib [abstract]. J Clin Oncol 2011;29;(Suppl 7):Abstract 320.
9. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomized phase 3 trial. Lancet 2011;378:1931–1939.
10. Hutson TE, Gallardo J, Lesovoy V, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal cell carcinoma. J Clin Oncol 2013;31(Suppl 6):Abstract LBA348.
11. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: results from a phase III randomized, open-label, multicenter trial [abstract]. J Clin Oncol 2012;30(Suppl 15): Abstract 4501.
12. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 2010;116:4256–4265.
13. Al-Marrawi MY, Rini BI, Harshman LC, et al. The association of clinical outcome to first-line VEGF-targeted therapy with clinical outcome to second-line VEGF-targeted therapy in metastatic renal cell carcinoma patients. Target Oncol, in press.
14. Hutson T, Escudier B, Esteban E, et al. Temsirolimus vs sorafenib as second line therapy in metastatic renal cell carcinoma: results from the INTORSECTtrial [abstract]. Presented at the 37th Annual ESMO Conference, September 28 to October 3, 2012. Vienna, Austria.