5 Minute JournalClub

Presurgical Feasibility of Bevacizumab for Nephrectomy-Eligible, Treatment-Naïve Patients with Metastatic Renal Cell Carcinoma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Advances in the biologic understanding of renal cell cancer and the emergence of clinical trial data with targeted therapeutic agents have resulted in the availability of novel treatment strategies for this challenging disease. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these rapidly evolving data sets. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with renal cell cancer.

LEARNING OBJECTIVE

- Recognize the effect of perioperative bevacizumab on long-term outcomes and intraoperative/postoperative morbidity among nephrectomy-eligible patients with metastatic renal cell carcinoma.

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5 MinuteJournalClub

As you may already know from our Post-ASCO 5-Minute Journal Club emails, one of the highlights of our steamy Miami summer was a series of daylong clinical investigator think tanks. Perhaps the most memorable of these fascinating events was a gathering of six clinical investigators whose brains we picked about one of the most rapidly evolving corners of medical oncology — renal cell carcinoma (RCC). The just-released **audio highlights program** of this adventure serves as the launch for a six-month integrated curriculum of activities designed to provide an array of interesting and relevant perspectives related to RCC management. A key focus of this comprehensive initiative is to better understand how investigators and practicing clinicians manage RCC, and to that end we recently conducted a national Patterns of Care study with 100 US community-based medical oncologists and the 12 curriculum faculty members, attempting to figure out how these physicians manage a disease that affects more individuals than CML, AML, CLL and ALL combined. Some of the RCC issues most asked about by oncologists in practice and discussed throughout the think tank include:

1. The role of nephrectomy for patients presenting with a primary tumor and metastatic disease, and the role of neoadjuvant systemic therapy for patients with unresectable or difficult-to-resect primary tumors

Two prior randomized trials demonstrated a benefit with nephrectomy for patients with metastases (Flanigan 2001, Mickisch 2001), but the studies are of questionable relevance in the new era of novel biologics. Ultimately, RCC could end up following the colorectal cancer paradigm, in which up-front systemic therapy is becoming standard for patients presenting with an asymptomatic primary tumor and metastatic disease. In RCC, this is far from a settled issue, as demonstrated by our Patterns of Care survey, in which 49 percent of the physicians surveyed would initiate systemic therapy for a patient with an asymptomatic primary tumor and mets, while 51 percent would send that same patient to nephrectomy as the first intervention. An ongoing Phase III trial hopes to address this critical and highly controversial question, but results will not be available for a while.

Neoadjuvant therapy seems to be even more problematic, and although **the new paper** by Jonasch and colleagues featured here demonstrates that 52 percent of patients experienced some regression of the primary lesion with single-agent bevacizumab, clinical investigators agree that preop systemic treatment, including attempts to convert primary tumors to resectability, should at this point be done only as part of a clinical trial.

2. Optimal sequence of systemic agents in metastatic disease

The FDA approval of bevacizumab/interferon makes this algorithm even more complicated, and the ODAC's recent vote unanimously supporting the approval of pazopanib likely paves the way for another player to join an already crowded field, which should be a good thing for patients. One tricky and unanswered issue is the contribution of interferon to the efficacy of bev, but there is no doubt about its adverse impact on quality of life in a palliative situation.

These days, virtually all investigators use a VEGF TKI — specifically sunitinib — as first-line therapy for metastases, but many use the mTOR inhibitor temsirolimus for patients with poor-risk disease. An important research question on the table is whether VEGF TKIs or mTOR inhibitors can be rationally administered as first-line treatment for metastatic disease regardless of risk status. In the future, the RCC model may mimic what's seen in endocrine therapy for breast cancer, where physicians choose from a menu of agents with similar efficacy but differences in tolerability.

3. Management of toxicities of biologic therapy

VEGF TKIs have only recently come into the oncologist's armamentarium, but RCC is also the first common tumor for which mTOR inhibitors are being regularly used. As evident from the **recent publication by Amato** evaluating the oral mTOR inhibitor everolimus, the spectrum of toxicities with these interesting agents is quite unlike any other treatment being used in contemporary medical oncology. Of particular importance is noninfectious pneumonitis, which in the Amato study occurred as Grade III or IV in 18 percent of patients. Our POC survey demonstrated that 40 percent of oncologists are not familiar with this complication and other toxicities associated with these agents, including hyperglycemia and hyperlipidemia.

4. The correlation, if any, between "dose intensity" of VEGF TKIs and treatment benefit, and how new agents like pazopanib and axitinib will stack up in terms of safety and benefit

Investigators have expressed concern that oncologists in practice may be prematurely bailing out on sunitinib or reducing the dose too quickly, and that this may be resulting in less benefit to patients than was demonstrated in clinical trials. While axitinib seems by indirect comparison to have similarly challenging tolerability issues as sunitinib, pazopanib holds the hope of a different and perhaps improved safety profile that may result in not only better quality of life but also perhaps greater efficacy by allowing full doses to be administered for longer.

Other critical issues being studied in current trials include the role of adjuvant systemic therapy and the use of combinations of biologics. Hopefully, the rapid pace of progress in RCC will continue and eventually result in substantial improvements in survival and cure rates for patients with this disease.

Be on the lookout for other activities in our integrated RCC curriculum as we attempt to efficiently provide information and perspectives about what is arguably the current forefront of solid tumor oncology.

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Presurgical Feasibility of Bevacizumab for Nephrectomy-Eligible, Treatment-Naïve Patients with Metastatic Renal Cell Carcinoma

Presentation discussed in this issue:

Jonasch E et al. **Phase II presurgical feasibility study of bevacizumab in untreated patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2009;27(25):4076-81. **Abstract**

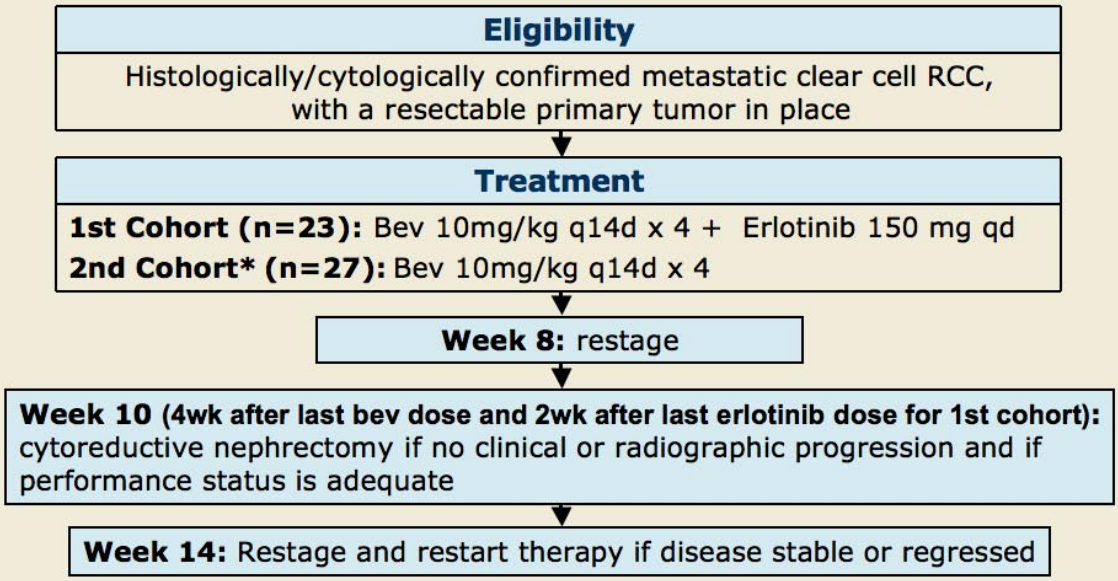
Slides from the presentation and excerpts from a related interview with Robert A Figlin, MD (October 7, 2009)

Introduction

- The role of cytoreductive nephrectomy (CN) for mRCC is not well established
  - Two randomized clinical trials demonstrated improved survival of patients who underwent nephrectomy in addition to treatment of metastases with immunotherapy (*NEJM* 2001;345:1655; *Lancet* 2001;358:966)
  - Little attention has been given to the timing of nephrectomy relative to systemic therapy
- Objectives of this single-site prospective study in patients with newly diagnosed, untreated mRCC with intermediate- and poor-risk features:
  - Determine safety of CN after antiangiogenic therapy with bevacizumab (bev)
  - Compare clinical outcomes attained with bev pretreatment to those of nephrectomy followed by antiangiogenic therapy
  - Determine whether bev pretreatment can select for benefit from CN

Source: Jonasch E et al. *J Clin Oncol* 2009; 27(25):4076-81.

Phase II, Non-Randomized, Single-Institution Study



* Study amended after report of no benefit to addition of erlotinib in randomized phase II setting (JCO 2007)

Source: Jonasch E et al. *J Clin Oncol* 2009; 27(25):4076-81.

Perioperative Outcome and Complications

- No report of intraoperative or perioperative complications attributable to study drug
- At four weeks postoperatively, 9 patients (20.9%) had delayed wound healing
  - No treatment delay (n = 5)
  - 20-21 days treatment delay (n = 2)
  - Grade 3, delayed wound healing, preventing resumption of trial therapy (n = 2)
  - Surgical intervention for fascial dehiscence three months after restarting bev therapy (n = 1)
- Postoperative death due to prolonged/challenging operation and deemed unrelated to study drug (n = 2)
- Median overall hospital stay = 5 days

Source: Jonasch E et al. *J Clin Oncol* 2009; 27(25):4076-81.

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Clinical Outcomes

Outcome Variable	Patients (n = 50)
Nephrectomy rate	**84%**
Median progression-free survival* (PFS)	11.0 months
Median overall survival (OS)	25.4 months
Median response duration	8.3 months
Overall response (OR) Complete response (CR) Partial response (PR)	12% 2% 10%

* Time to disease progression from time of first treatment

Source: Jonasch E et al. *J Clin Oncol* 2009; 27(25):4076-81.

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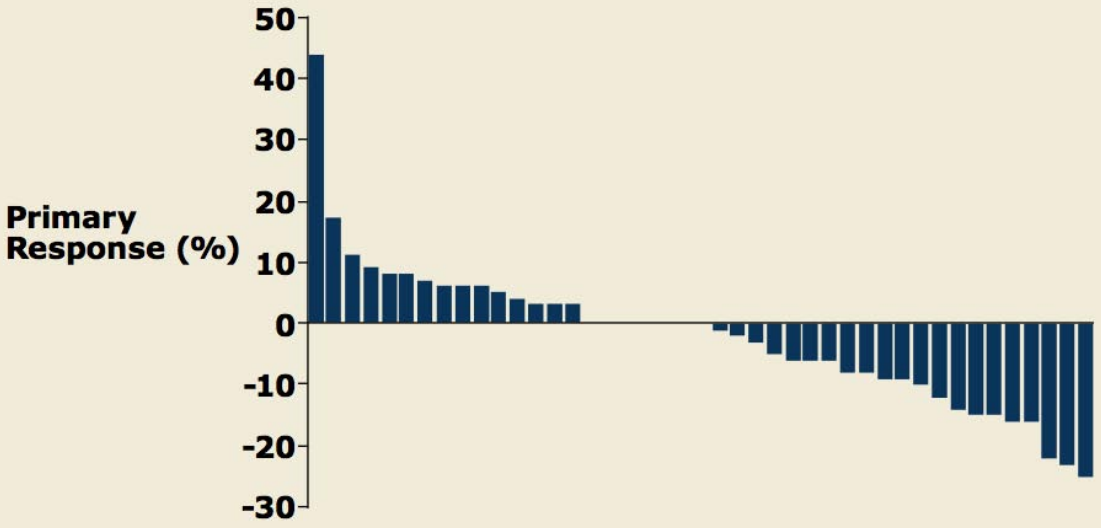
Waterfall Plot of Best Response in Primary Tumor Site to Presurgical Bevacizumab for mRCC



52% (23/45 patients with first restaging scans) had primary tumor reduction

Source: With permission from Jonasch E et al. *J Clin Oncol* 2009; 27(25):4076-81.

Discussion and Conclusions

- Presurgical treatment of mRCC with bevacizumab therapy yields clinical outcomes comparable to post-surgical treatment with antiangiogenic therapy but may result in wound-healing delays
  - Nephrectomy rate = 84%
  - Rate of delay in wound healing = 20.9%
  - Primary tumor regression rate = 52%
- In intermediate- and poor-risk populations, the observed PFS outcomes fall within the prospectively anticipated range for PFS, and OS is comparable to those from studies in the front-line setting
  - Median PFS: 11.0 mos; Median OS: 25.4 mos
- This study was unable to define the role of presurgical systemic therapy for selecting appropriate patients for CN due to lack of randomization and small sample size
- Prospective randomized trials exploring the definitive clinical benefit of this treatment approach are warranted

Source: Jonasch E et al. *J Clin Oncol* 2009; 27(25):4076-81.

ROBERT A FIGLIN, MD: The manuscript by Eric Jonasch summarizes the MD Anderson experience with presurgical bevacizumab in patients with metastatic kidney cancer who had their primary tumors intact. They report on 52 patients with clear cell carcinoma, who were enrolled during a three-year period, in whom they evaluated the benefit of bevacizumab for eight weeks prior to surgical resection. This presurgical approach is primarily one for the clinical research setting and should not be performed outside of a clinical trial.

The results of this trial as reported by Jonasch demonstrate several points. Approximately 18 percent of the patients had Memorial Sloan-Kettering Cancer Center (MSKCC) poor-risk disease, and that's important because we do not have evidence that bevacizumab has activity in these patients. Of the remaining population, 82 percent of the patients had intermediate-risk renal cell carcinoma — most of them with T3 to T4 disease. Ten patients had pathologic T1 disease, raising the question, What is the role for neoadjuvant or presurgical treatment for a patient with clinical T1 disease?

The authors demonstrated that they could administer bevacizumab safely, although the response rates were modest as expected from bevacizumab alone.

They observed little in the way of benefit with respect to the primary tumor, although the waterfall plot demonstrated that 52 percent had decreases in tumor size. Some of the patients' metastatic disease did have a reduction with one complete response of metastatic disease and 10 percent partial remissions.

Of note, the side effects were significant, remembering that many of these patients could have otherwise gone on to receive definitive surgical resection or systemic therapy for the treatment of their metastatic disease. The wound-healing delay that occurred in some patients is worrisome.

In fact, when one evaluates the data, three patients in the bevacizumab-alone group had delayed wound healing or dehiscence and two patients in the bevacizumab and erlotinib group died, which was not thought to be associated with the study drugs. So these patients likely had poor prognoses, and receiving this specific systemic therapy prior to definitive surgical resection might have not been the appropriate choice. Although the authors do not believe that the study drugs were associated with the deaths, they are still perioperative deaths in two out of 23 patients dying in close proximity to their surgery, which is a high mortality rate of 10 percent.

In summary, although bevacizumab can be administered safely in a presurgical setting with some clinical benefit — with respect to a modest reduction in the size of metastatic disease and in the size of the primary tumor — that has to be counterbalanced by wound-healing delays, perioperative morbidity, mortality and the as-yet-defined benefit of neoadjuvant therapies as opposed to treating definitively with surgical resection followed by systemic therapy or the appropriate systemic therapy alone.

Other clinical trials are investigating tyrosine kinase inhibitors (TKIs) prior to surgical resection with either sunitinib or sorafenib, but again, in the clinical setting for the practicing physician, presurgical treatment prior to surgical resection should be reserved for participation in a prospective, IRB-reviewed clinical trial and not as part of a standard regimen.

Dr Figlin is Acting Cancer Center Director, Arthur and Rosalie Kaplan Professor of Medical Oncology as well as Chair of the Division of Medical Oncology and Experimental Therapeutics at the City of Hope National Medical Center/Beckman Research Institute in addition to Associate Director for Clinical Research at the City of Hope Comprehensive Cancer Center in Duarte, California.