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Innovations and Challenges in Renal Cancer

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TRANSLATIONAL RESEARCH STUDIES IN RENAL CANCER: Neoadjuvant Therapy for Renal Cell Carcinoma Using Antiangiogenic Agents

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Introduction

The advent of therapies targeting the vascular endothelial growth factor (VEGF) pathway has revolutionized the care of patients with metastatic renal cell carcinoma (RCC). The currently approved agents either utilize humanized antibody to neutralize VEGF and remove this potent mitogenic signal (bevacizumab)[1,2] or small molecules which intercept the kinase signal of the receptor (sunitinib, sorafenib, pazopanib).[3-5] Each of these drugs has demonstrated, in differing contexts, an ability to reduce tumor size and bulk, delay tumor growth, improve progression-free survival, and in some cases improve overall survival.[6]

In spite of the successes that have been observed with these agents in patients with metastatic disease, these therapeutic strategies remain ultimately palliative, as complete responses are rarely observed and are not durable. Therefore, new strategies have been explored to integrate these pharmacologic strategies with surgical treatment as a multimodality

approach. Such adjunctive therapies have enjoyed widespread acceptance in the management of other cancers. The question of whether adjuvant therapy with an antiangiogenic regimen will similarly influence recurrence risk is currently the subject of several large clinical trials, the results of which are anxiously anticipated. The positive outcome of these trials will depend upon the effect of antiangiogenic agents to effectively eradicate micrometastatic disease, or to eliminate tumor cells via the non-VEGF receptor mediated kinase inhibition.

Rationale for neoadjuvant approach

The implementation of systemic therapy before resection of a primary kidney tumor raises several important questions, which are beginning to develop more clarity with the publication of several retrospective and prospective studies on this topic. (Table 1).[7-12,13-15] First, it is important to define the intent of pre-operative therapy, as RCC presents a unique scenario in which removal of the primary tumor, even in the face of overt metastatic disease, remains the standard of care for good performance patients based on the results of two randomized phase III studies in the cytokine treatment era.[16,17]

Table 1. Current experience with preoperative therapy in RCC

STUDY	N	STUDY TYPE	AGENT	RESECTABLE/ UNRESECTABLE	TREATMENT DURATION
Jonasch, et al.[10]	50	Prospective	Bevacizumab +/- erlotinib	Resectable	8 weeks
Cowey, et al.[11]	30	Prospective	Sorafenib	Resectable	4-8 weeks
Thomas, et al.[8]	19	Prospective	Sunitinib	Unresectable	To best response
Margulis, et al.[12]	44	Retrospective	Sunitinib Sorafenib Bevacizumab	Resectable	Variable
Thomas, et al.[7]	19	Retrospective	Sunitinib	Unresectable	Variable
Van der Veldt, et al.[14]	17	Retrospective	Sunitinib	Mixed	Variable
Amin, et al.[13]	9	Retrospective	Sorafenib +/- interferon Sunitinib	Mixed	Variable
Shuch, et al.[15]	4	Case Series	Sunitinib	Mixed	Variable
Bex, et al.[9]	10	Retrospective	Sunitinib	Unresectable	Variable

In this cohort of patients, the reasons to pursue pre-operative therapy prior to cytoreductive nephrectomy might include the opportunity to

reduce the size of the primary tumor for an optimal surgical approach,

gain systemic control of the disease before turning attention to management of the primary tumor, or

gauge the effectiveness of systemic therapy in an individual patient prior to embarking on a surgical procedure which may be of limited value in cases with rapidly progressive metastatic disease.

In the alternative case of locally advanced disease, the intent is clearly distinct. Here, although the risk of disease recurrence may be very high, the intent of surgical intervention is to achieve curative removal of the tumor. Therefore, neoadjuvant therapy may provide a valuable adjunct to surgery in this scenario by:

reducing the tumor size to permit a complete oncologic resection,

altering the primary tumor to improve the surgical approach (remove need for caval thrombectomy, convert open nephrectomy to laparoscopic or radical to partial nephrectomy, permit more complete nodal dissection, etc), and

downstaging the tumor and/or eliminating micrometastatic disease to reduce the risk for recurrence and improve the opportunity for surgical cure.

Current experience

The development of pre-operative antiangiogenic therapy remains limited to several relatively small phase II and pilot studies as well as case reports. This approach has been slower to be adopted into mainstream clinical practice precisely because the patient populations which might benefit from this multimodal approach are diverse and relatively infrequent. There is also significant uncertainty as to which patients (and for which intent) pre-operative or neoadjuvant therapy is most beneficial.

Ultimately, randomized studies are necessary to validate these adjunctive therapeutic approaches as superior to surgery alone. However, the available data sheds some light on several issues raised above. With regard to the management of patients presenting with synchronous metastatic disease considering cytoreductive nephrectomy, there is evidence from the Jonasch, et al. phase II study examining 50 patients treated with 8 weeks of bevacizumab and the Cowey, et al. study examining 30 patients treated with 4-8 weeks of sorafenib that the primary tumor can indeed be reduced in size with short-

term exposure to a systemic antiangiogenic to a degree that is roughly commensurate with the expected response of the metastatic lesions.[10,11] The data regarding conversion to a less morbid surgical approach is more limited, although several anecdotes have been reported. In particular, case reports suggesting that diminution of vena cava tumor thrombus can be achieved put forward a potentially very exciting setting for the benefits of pre-operative systemic therapy to include circumventing the need for a highly invasive and risky vascular intervention.[15,18,19] However, even this scenario must be considered with care, as case reports also detail the potential for tumor thrombi to progress during a short course of systemic treatment.[20]

The unique case of unresectable primary tumors in patients with metastatic disease was specifically addressed by a study exploring sunitinib treatment in 19 cases.[8] In contrast to the previous two studies in which the duration of preoperative treatment was fixed, this study implemented standard dose and schedule of sunitinib with a re-evaluation of surgical suitability every two cycles, and continual re-evaluation about the candidacy for surgery. Four of the 19 patients had undergone nephrectomy at the time the study was reported. With regard to the question of whether primary tumors can be diminished to a more amenable surgical target, the answer appears to be yes, at least in a portion of these patients.

These studies also address the opportunity to implement systemic therapy either as a modality to gain control of problematic metastatic disease or as a "litmus test" to assess the potential for cytoreductive nephrectomy to play a role. The three published prospective studies as well as retrospective studies suggest the primary tumor rarely progresses over the duration of pre-operative therapy. Thus using systemic therapy to first address symptomatic metastatic disease appears reasonable and does not preclude most patients from safely proceeding to surgery. In the Cowey, et al. study, all 30 patients proceeded to nephrectomy.[11] In the Jonasch, et al. study, 42 of 50 patients underwent nephrectomy.[10] As a "litmus test", the Jonasch, et al. study specifically categorized patients with responding or stable disease to proceed with nephrectomy, whereas those patients with progressive disease or rapid decline in performance status did not undergo surgery. In this study eight patients did not go on to nephrectomy. This may suggest the existence of a subgroup of patients who decline fairly rapidly, and thus may be spared a major surgical procedure whilst systemic and symptomatic management is prioritized. Ultimately, this use falls in the category of the art of managing an individual patient.

The bigger issues for the utilization of pre-operative therapy in the metastatic setting prior to cytoreductive nephrectomy concern timing: the timing of implementing surgery, the time drug should be held before surgery, and the timing of re-introduction of antiangiogenic therapy following nephrectomy. The evidence from metastatic treatment suggests that the greatest response occurs at between two and four cycles of treatment; therefore, treatment duration in that range might be extrapolated as a reasonable starting point.[21-23] Progression of metastatic disease is to be expected during the surgical convalescence period, and time to complete healing of the abdominal wound varies depending on the surgical approach and other co-morbid conditions that impact wound healing. Therefore, the time to re-instate systemic therapy is also an important decision to consider carefully.

The potential risks as well as implications for the non-metastatic disease patients are even greater. Here the immediate incentive is to reduce surgical morbidity while preserving curative opportunity. Roughly half of the patients in the Cowey, et al. study were non-metastatic, and several unresectable non-metastatic cases were included in the Thomas, et al. prospective study. These studies although involving small numbers of patients, provide a glimpse into some of the potential challenges faced in these settings. For tumors at quite high risk for recurrence that may be anticipated as challenging cases for surgery (T3, T4, or node positive tumors, solitary kidney) up front systemic therapy may be a necessary consideration. The data available from metastatic and non-metastatic cases encouragingly suggest that the surgical risk is not significantly elevated. Further, over the duration of a short up front course of treatment the potential for a delay of surgery for a few or several weeks to pose an immediate threat to the surgical containment appears to be negligible. Ultimately, the potential for neoadjuvant therapy to improve surgical cure is a tantalizing possibility, but the current data is too limited to offer any relevant insight.

Conclusions and current questions

Renal cell carcinoma management has reached a point in which the creative use of multimodality therapy provides an exciting venue for exploration. A variety of retrospective and three small prospective studies have provided important insights into the adjunctive use of antiangiogenic therapy with nephrectomy. All of these reports confirm that the primary tumor can be and often is responsive to systemic therapy. Perioperative risk did not appear to be increased significantly in any of the reports, although wound-healing issues were reported in greater numbers particularly with bevacizumab, consistent with the long half-life of this drug. Finally, in selected cases, tumors can be downsized sufficiently to accommodate surgery when previously considered ineligible for nephrectomy.

Other questions that have emerged include: Which agent provides the best tumor reduction and/or minimizes surgical risk for this multimodality approach? What is the optimal duration of treatment, time of treatment prior to surgery, and recovery period prior to reinstating treatment after nephrectomy? Can neoadjuvant therapy improve the curative potential of nephrectomy? Are there tumor or host-specific biomarkers, which may identify patients most likely to respond well to this therapeutic approach? Ongoing and future studies are needed to formally address these issues, so that multimodality therapy can be used to manage the unique needs of some patients with renal cell carcinoma.

Discussion

Dr. Atkins: I can see using neoadjuvant anti-angiogenic therapy for a patient with an unresectable primary tumor where

you would want to give systemic therapy ahead of surgery–because you cannot do a the surgery. But what is its usefulness outside of that setting from a clinical standpoint? This is a hot topic for urology key opinion leaders and urology conferences. What is your view of where we are at right now in terms of this as a therapeutic approach?

Dr. Rathmell: The question that I want to see answered is: can we reduce risk for recurrence by reducing the size of the primary tumor. I do not think that is completely heretical. We are using these drugs, thinking they can treat micrometastatic disease, for adjuvant treatment, so I think there is a possibility they can work in this setting. That is why I am very interested in the timing.

Dr. Atkins: But are you talking about wanting to try to give a year of therapy the same way they do in the adjuvant studies?

Dr. Rathmell: Well, where did a year come from? I don't know what the right duration is—a year or two months or four months. Also, when we approach a patient and look at what is the risk for recurrence, we estimate the patient's risk by their stage. I follow a patient who has a 4-cm tumor differently than someone who has a 12-cm tumor or who had renal vein invasion. So I think the question is, does the stage dictate the likelihood of already having micrometastatic disease, or does the stage impact the surgical resectability of that tumor? I do not know the answer. I think the trial that needs to be done is going to be all true neoadjuvant, all high risk and try to look and see if we can decrease risk for recurrence. I think that is where neoadjuvant therapy could have its greatest benefit.

Dr. McDermott: All that has been shown so far it that is that it is not a horrendous idea. But we are 10-15 years away from knowing whether it is a good idea or not.

Dr. Rathmell: I agree with that.

Dr. McDermott: But the problem is, while you are very calm and balanced in your presentation, some others who present this from the surgical side leave with the impression that urologists should be doing this. There is no evidence that this treatment makes it more resectable.

Dr. Rathmell: That is right. We ultimately need to do a randomized study but it is difficult to generate the enthusiasm and substantial support for a randomized study until it is proven that there is at least a suggestion of a risk of recurrence benefit in a smaller Phase II.

Dr. Kaelin: All you can do is establish feasibility.

Dr. Rathmell: Yes.

Dr. Atkins: I agree. It is feasible. But now you either do the experiment or not. Because there are so many ways this could be confounded, and you can get seduced into thinking you are helping the patients when you are actually not. So even if you show you can downsize a significant number of tumors a lot of them go to surgery, you already showed us an anecdote of somebody who you thought you were doing a world of good for only to have them relapse a few months later in a regional lymph node that they probably would have had resected otherwise.

Dr. Sznol: That is actually an excellent point, that surgeons do not usually change their surgical fields. You do not know that that tumor is shrinking away from the most distant extent. There still could be tumor cells out at the periphery. So you probably do not actually change the surgical field when you give neoadjuvant therapy.

And I have one other question. Is there really any evidence that the anti-angiogenesis agents given in a micrometastatic disease setting cure versus cause disease stabilization?

Dr. Rathmell: No. Not at all. None.

Dr. Sznol: So that is the larger problem with all of this. And there is no reason to believe that they should.

Dr. Rathmell: Right. I agree. But there is not evidence that they are not effective in this setting either.

Dr. Sznol: Because they are not directly cytotoxic.

Dr. McDermott: Right. And microscopic disease probably does not need a blood supply to stay alive for the year that it has got to stay alive while patients receive this therapy.

Dr. Hutson: And doing this cytoreductive approach makes no sense because we already know from our experience in the trials that absence or presence in the nephrectomy did not seem to predict, when we did the subset analyses, for a better response or a less response with the targeted agent. So I do not know that one should be taking this approach.

Dr. Sznol: So if you are going to give sunitinib, you should not be doing a nephrectomy?

Dr. Hutson: No, I am saying it makes more sense to resect if possible, then treat. You should not give the patients sunitinib to try to shrink the tumor, prior to resection.

Dr. Atkins: So let us talk about how you would design it from a research standpoint. What is the optimal way of sort of getting the most out of these studies?

Dr. Rathmell: You mean as a biomarker discovery tool?

Dr. Atkins: Yes, or mechanism of action tool or mechanism of escape. When Dr. Jonasch presented the MD Anderson experience at ASCO 2009 in looking at the post treatment specimen, one could not tell whether what we were seeing was the cells that survived the therapy, and therefore were de novo resistant, those cells exhibiting a biologic effect of the therapy, or those cells that had already acquired resistance to the treatment. And you cannot tell that, I guess, without having your pretreatment biopsy. And now you are adding all the variabilities of surgery to what you are seeing in the post specimen. These trials are hard to do and require a tremendous amount of cooperation, dedication and motivation. How do we do such studies so that we actually learn something about the mechanisms of these drugs and mechanisms of resistance?

Dr. Rathmell: I do not think we can address the development of resistance to these drugs with this kind of trial.

Dr. Stadler: And this is where some of my concern comes in. Let us say you wanted to do this. How would you design the trial? Well you would design a randomized trial where one arm gets just the surgery, one arm gets a very brief period of the VEGF pathway targeted therapy and then gets immediate surgery, one arm gets a longer-term therapy and then gets the surgery, and one arm gets the therapy until there is some kind of evidence of "resistance" by imaging or something, and then you get the surgery. So you have to have all those four arms — I mean that is at least a 400 patient trial. When you start thinking through the logistics of that, it becomes very, very complex.

Dr. Atkins: Well I think if you really want to look at a biomarker that is going to change as a result of your therapy then you would need to biopsy upfront and then perform a comparable early intra-operative biopsy for comparison.

Dr. Rathmell: Yes, I agree, that would be the most comparable sample to a pre-treatment biopsy.

References

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