

IN FOCUS: RENAL CELL CARCINOMA

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Adjuvant Approaches to Renal Cell Carcinoma

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H&O Why is there an urgent need to develop adjuvant therapies for kidney cancer?

CW The urgent need to develop adjuvant therapies stems from the large number of patients who present with more locally advanced disease and undergo surgical resection. Of these, a significant percentage will ultimately develop a relapse of their cancer. When their cancer does relapse, it is lethal; there is no cure for metastatic kidney cancer. Any approach clinicians can use to try to decrease the risk of relapse is certainly energy well spent. In terms of how the risk of relapse is defined, a variety of different parameters can be used. The most commonly used staging system is the tumor-node-metastasis (TNM) score, which categorizes tumors according to size and extent of spread from the primary tumor. For example, T1 and T2 tumors are those confined to the kidney and the separation is based on size, whereas T3 tumors are those starting to show evidence that the tumor cells are leaving the primary site, such as T3a, which extends into the fat, or T3b, which extends into the vein. The node status is also a prognostic factor: patients whose cancer has spread to the nodes have a significantly worse prognosis than those who do not have nodal disease. Staging is thus the most important way of assessing risk.

H&O What other methods are used to assess risk?

CW Other features of the tumor can be used to assess risk, such as the grade of the tumor, which refers to how aggressive the nucleus of the cancer cell appears under the microscope. High-grade tumors are associated with a higher risk of recurrence and death. Many investigators have developed nomograms or strategies that combine a

variety of different factors to express risk. The most well-known and often used is the University of California-Los Angeles Integrated Staging System (UISS), which includes patient performance status, TNM stage, and grade of the tumor. The performance status refers to how the cancer has affected the patient's life, and bad performance status is noted when the patient is significantly debilitated by the cancer (which has been shown to be prognostic). There are also other features and algorithms in use, such as Mayo Clinic's Stage, Size, Grade, and Necrosis (SSIGN) system, which utilizes a variety of pathologic factors, including the presence of histologic coagulative necrosis, which is associated with an adverse outcome. Algorithms also account for the histology of the tumor, including clear-cell, which is the most common, chromophobe, papillary, and others. Tumor histology is also predictive of outcome or risk of recurrence.

H&O Are molecular markers used in the assessment of risk in kidney cancer?

CW Research is currently focused on molecular markers that may augment the clinical paradigms in use for assessing risk. Molecules such as p53, Ki67, CAIX, B7H1, and B7H4 have been reported in the literature as potentially contributing to assessments of prognosis, but none has been prospectively validated. Research is headed in the direction of prospective validation.

H&O Once a patient's prognosis is defined, how is it used to select patients for clinical trials of adjuvant therapy?

CW Any adjuvant therapy is potentially and almost certainly going to have side effects, which can be considered the cost in an analysis of cost versus benefit. In patients who have a low risk of recurrence, with disease confined to the kidney, low-grade tumors, and favorable histologies, the argument would be that the negative effects of therapy do not outweigh the potential benefit because the risk is low from the outset. Conversely, patients with a high risk of recurrence are more likely to benefit from therapy, so the cost:benefit ratio favors administration of adjuvant therapy, despite its associated toxicities. Currently, there is no effective adjuvant therapy for kidney

cancer; standard of care, regardless of risk of recurrence, is observation. The clinical trials that are ongoing and are in the design stages are targeting high-risk patients for several reasons. First, these patients need novel approaches the most, but, second, in order to answer a question based on recurrence, an endpoint of the trial must be disease recurrence. A trial population composed of low-risk patients will not reach that endpoint, meaning the question will remain unanswered without a huge population size. For instance, if the risk of recurrence is 5% and a trial is attempting to show that an agent reduces that risk to 2%, the number of patients and the time needed to demonstrate this difference would be enormous because so few patients would recur. With high-risk patients, recurrence occurs more quickly, which leads to trials conducted more expeditiously. But high-risk patients are not as common as patients with localized disease in this setting, meaning accruing sufficient numbers of patients to a trial can be a challenge.

H&O What are the hypotheses for the lack of success with past attempts to develop adjuvant therapies for kidney cancer?

CW Many approaches have been tried in the past as adjuvant therapies for kidney cancer. The paradigm for research in adjuvant therapy is to test the drug initially in the metastatic setting and if it demonstrates efficacy, it is then researched in the adjuvant setting to evaluate its effect on risk. Therefore, this paradigm implies that the biology of locally advanced renal cell cancer is the same as that of metastatic renal cell cancer, resulting in the agent achieving the same effect in each setting. However, it is unknown whether the biology of each setting is the same. There are some interesting data showing that the biology may in fact be different, meaning the agent that is effective in one disease state may not be effective in the other. Furthermore, approaches that have been tested, such as hormonal therapy, immunotherapy, and chemotherapy, are not particularly effective in the metastatic setting, so it seems even less likely that these minimally effective approaches would be more effective in the adjuvant setting. In summary, the disease states, whether locally advanced or metastatic, may be very different biologically, and we have not discovered agents in either setting that show great efficacy.

Trial design also plays a role in the lack of success of previously researched approaches. One recent trial of the vitespin vaccine therapy (Oncophage, Antigenics) had notable problems in that a significant number of patients enrolled on the trial had baseline disease and were not truly locally advanced, but rather were already metastatic. Thus, these patients, who composed a large portion of

the patient population, did not count toward the final results, significantly affecting the statistical power of the trial and undermining the researchers' ability to achieve a useful result from the trial. The trial was designed, as is a common scenario, to enroll patients with localized or locally advanced disease. In many cases, after surgery and restaging, the investigators did not find evidence of metastatic disease and the patients were enrolled. However, at the end of enrollment, when the pathology films were reviewed independently—by blinded radiologists with no vested interest in the patients—it was found that significant numbers of patients did in fact have evidence of metastatic disease. But this finding occurred too late because the patients were already enrolled. The ideal process would be to have a central review of pathology prior to enrollment, but this process would be difficult logistically.

H&O What new approaches are currently under investigation in the adjuvant setting?

CW Tyrosine kinase inhibitors and an antibody are currently under investigation. The trial investigating WX-G250 (Rencarex, Willex) completed enrollment recently. This agent is an antibody against protein CAIX, which is highly expressed in clear-cell renal carcinoma. WX-G250 has shown some efficacy in phase II trials in the metastatic setting, which is the logic for bringing it into the adjuvant setting. It is unclear whether this agent will show efficacy in this setting. Eastern Cooperative Oncology Group (ECOG) 2805 (Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected Renal Cell Carcinoma; ASSURE) is testing sorafenib (Nexavar, Bayer/Onyx) and sunitinib (Sutent, Pfizer) versus placebo for 1 year, and though results are not yet available, significant rates of toxicity have been observed. Another trial in the United Kingdom is comparing two schedules of sorafenib (3 years vs 1 year) to placebo. There is another trial in Europe, which is comparing sunitinib to placebo.

The trial of heat-shock protein 96, the vitespin vaccine, was recently completed. In the final analysis, the researchers were unable to show a benefit in disease-free or overall survival in the patients who received the vaccine versus those who were observed only. In subset analyses, there appears to be evidence that the vaccine benefited select populations with intermediate-risk disease. The high-risk patients did not derive benefit from the treatment, and controversy exists as to whether subset analyses generally are valid beyond the purpose of generating hypotheses. There was a single-center trial conducted at The University of Texas M. D. Anderson Cancer Center using thalidomide (Thalomid, Celgene), which was a dif-

ficult trial due to the side effects associated with this agent. Although the trial population was quite small, there does appear to be an improvement in cancer-specific survival with 2 years of thalidomide after surgery in patients with kidney cancer. There are phase II data with lenalidomide (Revlimid, Celgene) in the metastatic setting, but the findings were not considered positive enough to warrant research in the adjuvant setting.

Finally, there are no ongoing trials of bevacizumab (Avastin, Genentech) in the adjuvant setting, but I believe there should and could be such trials in the future. The main impediment to investigating additional agents in the adjuvant setting by initiating new trials is simply that there are not large numbers of patients available. Ten trials testing ten different agents in this setting would likely result in ten incomplete trials that were unable to accrue sufficient numbers of patients. Instead, the renal cancer community has tried to prioritize certain research. Many of us are devoted to completing the ECOG 2805 trial before moving on to the next agent. Bevacizumab is, however, an option for future research. The greatest potential downside, which hampered the trial of WX-G250, is that the formulation of the drug is intravenous, requiring patients to come to the hospital. A randomized, placebo-controlled trial that asks patients to consent to the possibility of receiving intravenous saline once a week for 24 weeks could pose a challenge.

H&O How does neoadjuvant therapy fit into the treatment algorithm in this setting?

CW There are ongoing clinical trials studying neoadjuvant therapy in both the locally advanced and metastatic settings. In the locally advanced setting, there are two notable trials. The most interesting trial, at Cleveland Clinic, is classifying patients as “unresectable”—though that classification is debatable—and treating them with sunitinib. If these patients demonstrate a response of primary tumor regression, which may potentially facilitate resection, patients are taken to surgery. This design is appealing, but the controversial aspect is that the most effective treatment for locally advanced renal cancer is undoubtedly surgery. If patients receive neoadjuvant therapy, their surgery—the only potentially curative treatment—is delayed. Thus, if the patients do not respond or show a response while also metastasizing, it is highly questionable whether the neoadjuvant approach has resulted in benefit. Another issue, which needs to be

examined further, is when to schedule surgery in the setting of neoadjuvant therapy. If a patient is responding to neoadjuvant therapy, clinicians may be reluctant to stop the therapy in order to perform surgery; conversely, if a patient is not responding and becoming refractory, clinicians may be reluctant to resect the patient because of the risk of postoperative disease progression. Still, neoadjuvant therapy is attractive because it may downstage the tumor and it comprises a limited amount of therapy, unlike the therapy in the 1-year or longer adjuvant trials. As with all treatment algorithms, the cost:benefit ratio must be evaluated on a patient-by-patient basis, in consultation with the patient. Some patients may consider a 20% risk of recurrence to be surprisingly small and others may consider it intolerable. A patient’s willingness to face side effects will be affected by his or her perception of risk.

H&O What is your overall view of the progress of research into adjuvant approaches?

CW In conclusion, research into adjuvant therapy is ongoing, and there are promising agents, but it remains to be seen whether efficacy will be demonstrated. The ECOG trial will generate interesting results, and there are other agents worthwhile to investigate in the adjuvant setting in the future. Toxicity remains a major problem. It could be argued that one of the appealing attributes of vaccine therapy was its lack of side effects but I would counter that argument by saying that a lack of side effects could indicate a lack of activity. A patient’s perception of risk will clearly affect whether a clinician administers adjuvant therapy. Until final results are available from ongoing trials, standard of care remains observation.

Suggested Readings

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