Management of Metastatic Renal Cancer

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Kidney cancer, medical management, review

Abstract
The purpose of this article is to review the systemic management options for patients with metastatic renal cancer. We reviewed the literature regarding systemic management of metastatic renal cancer. Treatment options of chemotherapy agents, immunotherapy, molecularly targeted agents, allogeneic stem cell transplantation, vaccines, and other manipulations of the immune system are discussed. No chemotherapy agent used alone or in combination has consistently produced responses to substantiate its routine use. Interleukin-2 (IL-2) and interferon-α (IFN-α) have shown response rates ranging from 10% to 20%. Some studies have shown that retinoids may enhance the antitumor activity of IFN-α. Molecularly targeted agents and angiogenic agents are being actively pursued and several studies are showing response rates above 30%. Although nonmyeloablative allogeneic stem cell transplantation shows some promising results, they also have limitations to its use. Therapy strategies that incorporate vaccines as part of comprehensive immune manipulations are also being studied. The systemic treatment of patients with advanced renal cell cancer continues to be a significant challenge. Immunotherapy treatment has shown response in up to 20% of patients. Unfortunately, most do not respond. The current technologies are promising and may be the key step for introduction of better treatments for renal cancer care. (JNCCN 2005;3:105–113)

The incidence of renal cancer is rising slowly, including metastatic cancers. For the United States in 2004, estimates are 35,710 new cases (about 3% of solid tumors) and 12,480 deaths. Many patients never undergo potentially curative surgery because tumors are clinically silent for much of the course, with diagnoses delayed until the disease is advanced.

Prognosis for recurrent or metastatic renal cell carcinoma (RCC) is often poor, and many series show a median survival of less than a year. Prognostic estimates are valuable in directing therapies as well as for comparing treatment groups in the literature. Motzer et al. described five independent prognostic factors derived from retrospective data in a readily applied stratification scheme. Using some of the same factors, Zisman et al. developed an alternative mathematical model for individual prognosis for application to metastatic or non-metastatic patients (Table 1).

The SWOG and EORTC trials compared nephrectomy followed by interferon with interferon alone in patients with good performance status. They show an approximately 6-month median survival improvement attributable to nephrectomy. This result, combined with the observation that nephrectomy status is a major prognostic factor, has been the basis for a standard of routine consideration for nephrectomy of patients with metastatic disease at presentation. Aside from performance status, other factors that influence the value of nephrectomy as initial therapy include the extent to which surgery would debulk the total tumor burden and the possibility of alleviating or preventing pain, hematuria, or asthenia. Factors against surgery may include metastatic disease, such as brain tumors, and initial uncertainty as to the natural rate of the cancer growth. The bias is that slower growing tumors derive the most benefit. Inevitably, practice patterns and patient preferences vary.

In this discussion, we address highlights of several paradigms for systemic treatment. The conventional drug approaches include (1) chemotherapy using “cytotoxic” drugs, with many off-study and some on-study options available; (2) immunotherapy based on cytokines, with many schedules, including clinical trials and in combination with other drug classes; (3) molecularly targeted agents, including angiogenic targets, with several pivotal trials ongoing. Treatments integrating cellular products, generally limited to within clinical trials, include (4) allogeneic stem cells...
and (5) vaccines and other complex manipulations of the immune system, which combine vaccines, cytokines, and cellular therapies.

### Chemotherapy Drugs

No agent or combinations from this class have shown consistent enough responses to meet a standard for routine initial use. The extent of this negative experience can be appreciated, for example, in a table showing outcomes of 33 chemotherapy agents between 1990 and 1998, studied in 1,347 patients in 51 phase II trials. Conversely, some drugs appear to be useful for some patients. Among the more extensively studied are 5-fluorouracil (5-FU) and related drugs floxuridine and capcitabine.

The reported results for a combination of continuous intravenous infusion of 5-FU for 21 days with weekly gemcitabine (600 mg/m²) was 7 of 41 partial responses (PR) and 5 of 41 cases of stable disease. Extensions of the 5-FU/gemcitabine base with cisplatin, thalidomide, or interferon (IFN) and interleukin-2 (IL-2) also had isolated responses without suggesting superiority.

Response rates up to 20% were reported with a circadian schedule of intravenous floxuridine. Subsequent similar trials showed response rates of 0% to 14%. A phase III trial using circadian versus flat continuous infusion showed an overall response rate of 9%. In general, responses were not durable.

The oral drug capcitabine is converted in a three-enzyme pathway to 5-FU, potentially concentrating in tumor. With use of capcitabine as a single agent, Wenzel et al. reported on an Austrian series in which previous immunotherapy failed. They reported 2 of 26 partial responses, 5 of 26 minor responses, and 13 of 26 stable responses, for an overall rate of at-least-stable disease in 77% of cases. A U.S. report using capcitabine in combination with low-dose interferon showed only 32% of cases achieving stable disease.

Capecitabine has also been used in combination with gemcitabine, with response rates seen in about 20% of patients. The cooperative group trial CALGB 90008, reported at ASCO in June 2004, tested this combination and noted 15% (confidence interval [CI], 7% to 27%) partial responses. Other gemcitabine-including combinations are in development, such as with oxaliplatin. Capecitabine is component of an ongoing trial, together with GTI-2040, a ribonuclease-reductase antisense drug.
Troxacitabine is a non-natural nucleoside analogue that interferes with mammalian DNA polymerase. A National Cancer Institute (NCI)-Canadian phase II trial reports 2 of 33 major responses and a high frequency (21/33) of patients showing stable disease. This may be a basis for more trials.10

Another emerging group of cytotoxics are the epothilones, related to derivatives from Sorangium celulosum soil bacterium.21 Epothilones act at the same site of contact with tubulin as the taxanes but may not have cross resistance. Two that are undergoing clinical testing are epothilone EPO906 (Novartis, East Hanover, NJ) and Ixabepilone (Bristol-Myers Squib, New York, NY). The latter agent is part of an NCI single-arm, phase II trial for RCC; a 10% partial response rate was reported in June of 2004.21

**RCC That Is Not Clear Cell**

About one quarter of kidney cancers are the not clear cell subtype. Among these are sarcomatoid, papillary, collecting duct, and chromophobe as well as transitional cell cancer of the renal pelvis, which is usually treated similarly to bladder urothelial cancer. Although the experience in treating infrequent subtypes lags because of lower numbers of patients, some responses emphasizing conventional cytotoxic combinations have been reported. These remain of interest because the immune-directed approach has been seen to be potentially less active in cancers in the kidney that are not clear cell subtype.

Collecting duct cancers are among the most aggressive cancers. Some combinations that have been applied include platinum-based doublets and doxorubicin plus gemcitabine. ECOG 2803, a recently opened phase II trial, will study carboplatin and paclitaxel for collecting duct tumors.21 Sarcomatoid renal cancer can also have an aggressive course. Based on evidence from case reports, doxorubicin-based treatments for sarcomatoid-type kidney cancer may have significant benefit in the occasional patient. However, a trial of doxorubicin plus ifosfamide reported only one of 25 patients with stable disease.24 An ECOG phase II trial (8802) is testing a combination of doxorubicin and gemcitabine for sarcomatoid renal cancer.

**Immunotherapy**

Remarkably, in rare cases renal cancer triggers an immune response that induces remission. Various immunotherapeutic approaches have been proposed to amplify or replicate this response. Among cytokine drugs, the most consistent responses are with IL-2 and IFN-α.

**Interleukin-2**

In the 1980s, IL-2 was evaluated for RCC in combination with lymphokine-activated killer cells (LAK). Randomized trials comparing the combination of LAK and IL-2 with IL-2 alone showed that high-dose IL-2 used alone was as effective as the combination treatment.25 Although lymphocyte therapy, including LAK cells or expanded tumor-infiltrating lymphocyte (TIL) cells remain of interest, contemporary off-study use of IL-2 is mostly without these cellular additions. In 1992, the Food and Drug Administration approved high-dose bolus IL-2 for treatment of metastatic RCC based on multicenter phase II trials in which 12 of 255 complete responses and 24 or 255 partial responses (14% overall, 38% with bulky tumor) were seen. Patients who experience complete response have remarkably durable disease-free survival. The median duration of response for patients who experienced response was 54 months (range, 3–107 months); however, median whole group survival was only 16 months. Because of its complications, notably hypotension and required use of a ward that can accommodate pressor use, as well as its restriction to patients with good performance status, the applicability of high-dose IL-2 remains limited.26–27

A more recent phase III randomized study from the National Cancer Institute (NCI) compared high-dose bolus IL-2 (720,000 IU/kg/dose times 14 doses/course) with a low-dose IV (72,000 IU/kg/dose), and a third arm with low-dose subcutaneous IL-2 (week 1 consists of 5 days of 250,000 IU/kg/day, weeks 2 to 6 consist of 5 days of 125,000 IU/kg/d). For the first comparison (high-dose/low-dose intravenous) response rates favor high-dose (21% vs. 13%) with a trend to a more durable response for high dose, but with lower toxicities in the low-dose group. The high-dose bolus versus subcutaneous comparison showed the high-dose arm again significantly better in response rate (21% vs. 11%). Again, the lower-dose was better tolerated and the subcutaneous treatment can be offered as an outpatient regimen.28

**Interferon-α**

This cytokine also has been studied extensively, with approval for use in treating renal cancer outside the United States. Considering a variety of schedules, the
overall response to INF-/H9251 monotherapy appears about 15%, although some large series, such as in the control arms of randomized studies, have recorded much lower response rates (IFN vs. IFN and thalidomide or nephrectomy then interferon vs. interferon). Interferon responses may be delayed, with time to response of four months. Most responses are partial and last less than a year; however, some long-term survivors are reported. Prognostic factors for a more favorable outcome with IFN-alpha treatment include performance status, nephrectomy, less than 12 months from initial diagnosis, and lung-predominant metastases. Groups with more favorable features may show response rates up to 30%.

Interferon-alpha has also been studied in combination. A positive phase III trial comparing vinblastine with and without IFN-alpha-2a reported a median survival in the combination arm of 68 versus 38 weeks without interferon. Because other trials have shown absence of vinblastine activity as a single agent, the benefit is attributed to IFN-alpha. Pharmacokinetic modifications of IL-2 and IFN-alpha with pegylation, which accommodates once per week dosing, have been developed. Phase I and II trials of Pegasys (Roche) and PegIntron (Schering) in treatment of RCC showed some responses.

**Interferon-Interleukin-2 Combinations**

Theoretically, IFN-alpha up-regulates expression of HLA class I and of tumor-associated antigens, increasing the immunogenicity of tumor cells, so as to sensitize for IL-2-mediated cell lysis. Multiple schedules, often with 5-FU, have been described, with response rates that vary from 2% to 38%. Schedule-detail and patient selection appear very important.

Among newer prospective randomized tests of more complex (all outpatient) schedules is the German trial comparing IFN-alpha plus IL-2 (subcutaneous) plus 5-FU (intravenous) versus that combination plus oral 13-cis-retinoic acid versus IFN-alpha plus vinblastine (intravenous). The authors found better survival in the first and second arms (25 and 27 months) compared with the third arm (16 months; P = .044 for first vs. third; P = .023 for second vs. third comparisons) and that all these schedules were well tolerated.

A phase III trial by the Cytokine Working Group compared intermediate-dose IL-2 plus INF-alpha with high-dose IL-2. A preliminary report favors the high-dose IL-2 arm (25% vs. 12% overall response), with a trend toward higher median survival and similar median response duration.

**Retinoids**

Retinoids bind to retinoic acid receptors in the RAR and RXR family. They may impact on both the immune system and the cancer cell physiology. Several phase II trials have shown that some retinoids may enhance the antitumor activity of IFN-alpha. A phase III trial showed an absence of benefit of 13-cis-retinoic acid plus IFN-alpha when compared with IFN-alpha alone.

**Molecularly Targeted Agents, Including Angiogenic Targets**

Patients who experience relapse after treatment with IL-2 or IFN or who are avoiding these agents because of toxicity risk frequently consider alternative treatments such as experimental agents. Some cancers have had shown a large response to molecularly targeted drugs, and intense investigation is underway to find the best target to drug pairs for RCC.

Among distinctive features in clear-cell cancer is deficiency of the von-Hippel-Lindau protein (pVHL), which is mutated or silent in a majority of specimens. In the context of impaired pVHL function, metabolism (destruction) of hypoxia inducible factor protein (HIF-1alpha) is impaired, causing a dysregulated activity of the genes bearing the hypoxia response element (HRE) to which the HIF-1alpha complex binds. Vascular endothelial growth factor (VEGF, VEGF-A) is regulated by HRE. Interference with VEGF/VEGF-receptor pathways may be relevant as anti-tumor, anti-angiogenic, or immune-modulation pathways, because some of the same pathways and receptors are present in each of those cell types.

Drugs that deplete VEGF from the plasma include the antibody drug bevacizumab (Avastin, Genentech, South San Francisco, CA) and VEGF-Trap (Regeneron Pharmaceuticals, Tarrytown, NY), a recombinant protein with components of the Fc portion of human IgG, and VEGF-R1 and VEGF-R2 extracellular domains. A small molecule tyrosine kinase inhibitor of VEGF-R2 (and other tyrosine kinases) is Su011248; PTK-787, manufactured by Novartis, also inhibits this target.

The epidermal growth factor receptor (EGFR) is another surface receptor tyrosine kinase. It is blocked by agents such as gefitinib (Iressa, AstraZeneca, Wilmington, DE), erlotinib (Tarceva, Genentech), and by the antibody...
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drug cetuximab (Erbitux, BMS and Imclone in the U.S.; Merck KGaA in Europe). A relationship that may have therapeutic implications is that ligation of EGFR may be associated with VEGF expression.

An early trial of single-agent gefitinib in RCC showed no major response (0/16). A later report identified 8 of 21 patients treated with single-agent gefitinib had stable disease. Erlotinib is in active testing for RCC; a single-arm phase II trial testing the combination of erlotinib and bevacizumab was presented at the ASCO meeting in June 2004. Of the 58 patients enrolled, 21% showed partial response and 66% had at least stable disease. A manufacturer-sponsored trial of bevacizumab without or with erlotinib in first-line therapy is anticipated.

A randomized phase II trial at NCI compared every-two-week bevacizumab 10 mg/kg and 3 mg/kg and placebo. It was stopped early, when 116 patients had enrolled, because an interim analysis showed significant prolongation in time to progression in the 10-mg/kg arm (4.8 vs. 2.5 months on placebo). Thirty percent of patients in the bevacizumab arm were progression-free at eight months. A CALGB phase III trial (90206) comparing interferon without versus with bevacizumab is now underway. IL-2 plus bevacizumab is now underway.

Su11248 (also known as Su011248; Pfizer) is a small-molecule tyrosine kinase inhibitor of VEGFR as well as platelet-derived growth factor receptor (PDGFR) and of flt3 and c-kit. Favorable data of a phase II trial were presented at ASCO in June of 2004. Of the 63 accrued patients, 33% had partial response and 37% had stable disease of at least three month’s duration. A manufacturer-sponsored phase III randomized trial comparing Su11248 to interferon is open.

The intravenous drug CCI-779 (Wyeth) is an inhibitor of mTOR (mammalian target of rapamycin). This target is downstream in the signaling pathway compared to VEGFR or EGFR. A randomized phase II trial using three different dose levels in 111 patients showed response rate of 7%, plus 26% of patients showing minor responses. Most encouraging, the median time to progression was 5.8 months and the median overall survival was 15 months. When patients were segregated by prognostic risk factor criteria, patients with intermediate and poor prognosis had derived the most benefit. A currently open, manufacturer-sponsored phase III trial will compare CCI-779 versus interferon versus both in the patients from those risk-categories.

Finally, sorafenib (Bay 43-9006) is a small molecule that inhibits b-raf, c-raf, PDGFR, VEGF-R2, c-kit, and flt-3. The initial testing for RCC was in a single-agent randomized discontinuation phase II trial; in the trial design, after 12 weeks of treatment, patients with more than 25% improvement were assigned to continue treatment, patients with progression of disease would discontinue treatment, and patients with stable disease (< 25% worse, < 25% better) were randomized between placebo or continued treatment. In June 2004, researchers reported that of the 203 patients accrued, 89 were evaluable, and only 37 had discontinued secondary to disease progression. Updated follow-up information on the rest of the cohort can be anticipated. A manufacturer-sponsored double-blind (sorafenib vs. placebo) phase III trial is restricted to second-line therapy.

Thalidomide

Thalidomide may have antiangiogenic or immune modulation mechanisms. In several single-arm studies, the response rate was low, but stable disease (SD) was reported in up to 56% of patients at six months. In a more encouraging report, Amato et al. describe a single-institution phase I to II trial with a combination of thalidomide (200 mg/d) and low-dose, subcutaneous IL-2 (7 million/m^2/dose, times 20 doses). In that study, 41% of the 37 patients enrolled in the phase II part showed an objective response. A different schedule (100 mg/d thalidomide and IL-2 at 250,000 IU/kg/dose, then 125,000/kg/dose over 6 weeks) had a lower response rate.

An ECOG phase III trial (E2898) of low dose IFNα-2b versus combined with thalidomide was presented in June of 2004. It showed only 2.2% (control) and 6.5% (combination) responses. The overall survival nonsignificantly favored the control arm. This experience is less encouraging for development compared to the tyrosine kinase inhibitors.

Vascular Targeting Agents

Another strategy is to attack existing tumor-vessel endothelium, as opposed to the development of new blood vessels. Vascular targeting agents, some of which are chemically related to colchicine, theoretically may cause the flat endothelial cells lining tumor vessels to round-up and block blood flow, causing tumor infarction. The high tumor vessel density of kidney cancer is a basis for interest in applying this class to RCC. Examples include ZD6126, Combretastatin-A-4-phosphate, and ABT-751.
Nonmyeloablative Allogeneic Stem Cell Transplantation

Engrafted allogeneic lymphocytes can induce graft-versus-tumor effect in patients with hematologic and solid tumors.58 The known susceptibility of RCC makes it appealing for translational development of useful graft-versus-tumor effect. In the first major publication, Childs et al. noted that 9 of 19 subjects with refractory metastatic RCC treated with nonmyeloablative transplant showed a response. Three had complete responses. However, 2 of the 19 patients died of treatment-related problems.59 Key features currently include: clear cell subtype; full sibling with HLA-match; limited, slow rate of tumor growth; and few comorbidities. Experience continues to evolve in U.S. and international trials.60–62

Vaccines

The fundamental concept of vaccine therapy is that the tumor will be susceptible if the immune system can be correctly oriented. Many vaccine strategies have been developed for renal cancer; some use products based on single peptide epitopes, tumor-specific proteins, and tumor cell lysates. Others use intact tumor cells that have been modified by exposure to cytokines, radiation, or modified to produce immunostimulating cytokines such as granulocyte macrophage-colony stimulating factor (GM-CSF) or the dendritic cell surface protein B7.1 (CD80). Finally, autologous dendritic cells, which may be loaded with antigen using synthetic proteins, nucleic acids, tumor lysates, or other means, including tumor-cell/dendritic cell fusion have been used. In animal models, regression of established tumors and protection from tumor inoculation have been attained many ways. Presently, no anticancer vaccines are licensed in the United States, but a number of trials covering many dimensions of the problem have been completed. The positive experience of the German phase III randomized trial of the aTL vaccine (LipoNova), consisting of autologous cells cultured with tocopherol and IFN-γ, was reported by Jocham et al. in 2004.63 The report describes improved progression-free survival with use of the vaccine, although some methodologic issues and the absence of overall survival data again reinforce understanding the limitations on the practical impact attributable to vaccine approaches at this point.

Conclusions

The systemic treatment of patients with advanced renal cell carcinoma remains challenging. Natural history features (Table 1) rather than medical treatment decisions continue to dominate prognosis. Nephrectomy in the face of metastatic disease has, for many cases, become more widely accepted as beneficial. Cytokine treatments have achieved responses, some of them long lasting, but most patients do not show a response to treatment, and incomplete responses may have limited durability.66,67 Only a minority of patients respond well to off-study (or “control-arm”) treatments such as IL-2 or IFN-α; however, for the occasional patient with excellent outcome, the cytokine-only approach is worthwhile.

Current technologies in testing appear promising. Strategic clinical trial design and participation remain a priority to capitalize on new agents and treatment paradigms. The practicality of trial participation may be contingent on the treating physician’s familiarity

Table 2 Internet Resources for Trial Information

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Interest remains high, although the chance of major clinical response to an isolated vaccine approach appears low, as discussed in a recent editorial.65 Similarly, for practical patient-care purposes, “scientific” enthusiasm for laboratory endpoints such as “lymphocytes with detectable specific anti-tumor activity” is important mainly for future trial design, but may not be clinically important. As in the experience with cytokine treatments, phase II trial designs with complex treatments requiring high compliance and limitations to slower-than-average disease natural history are not immediately generalizable. Building on this experience, researchers have noted interest in strategies that incorporate vaccine as part of a comprehensive immune manipulation, which may involve lymphocyte infusion, dendritic cell maturation, cytokine amplification, and others.
with the current trials (Table 2) as well as patient education about palliative versus interventional perspectives at each stage of the disease process. In considering the clinical impact of novel agents, one must formally consider that tumor-size stabilization may not directly imply survival or clinical benefit. Therefore, the need for phase III trials continues despite optimism from phase II experiences. At the close of 2004, an unprecedented five major randomized trials of targeted drugs (Table 3) are underway that may solidify a paradigm shift toward better-tolerated, frequently efficacious treatment for RCC. Treatments involving host preparation, introduction of anti-tumor lymphocytes, vaccines, and cytokine combinations mark increasingly sophisticated immune manipulations that continue to be of interest as well.

### References


