Management of Renal Cell Carcinoma

Drs. Wolchok and Motzer provide a succinct, timely review of the diagnosis and management of renal carcinoma. The article leads us to ask a number of questions: What factors account for the major increase in the incidence of renal carcinoma? How has surgical management evolved with the advent of newer operative techniques? What role, if any, does chemotherapy play in the treatment of this disease? What is the current status of and future outlook for immunotherapeutic approaches?

Risk Factors for Renal Carcinoma

The etiologic factors responsible for renal carcinoma have not been as well defined as have factors in other malignancies. A recent report by Yuan et al found a significant increase in the risk of developing renal carcinoma with tobacco use (odds ratio, 1.35; 95% confidence interval [CI], 1.14 to 1.60).[1] The risk correlated with current use and with an increasing number of cigarettes smoked per day. This study helps confirm the role of tobacco in the development of renal carcinoma. Mutations of the von Hippel-Lindau (VHL) gene have also been implicated in the development of clear cell and granular histologic subtypes. The mechanism by which these mutations lead to such tumors has been further defined recently.[2] The normal VHL gene product, pVHL, suppresses the synthesis of carbonic anhydrase IX, also known as G250. The mutated pVHL no longer suppresses G250, which leads (by still obscure means) to vascular endothelial growth factor expression and resultant hypervascularity. Although the mechanisms remain to be defined, it is becoming clear that specific types of VHL mutations influence tumor biology, as seen in the acute leukemias, where specific cytogenetic abnormalities lead to characteristic clinical syndromes. Hopefully, further studies will lead to more targeted therapies, such as with all-trans-retinoic acid (ATRA [Vesanoid]) for acute promyelocytic leukemia. Furthermore, recent evidence implicates occupational trichloroethylene exposure in the development of renal carcinoma with specific VHL gene defects. However, the validity of this exposure risk is questioned by some.[3] Thus, as more becomes known about the environmental and genetic influences on the pathogenesis of renal carcinoma, the disturbing trend of an increase in incidence can hopefully be reversed with more efficient prevention and detection efforts, perhaps by molecular screening of high-risk, targeted populations.

Surgery

Surgery—a mainstay of therapy for localized renal carcinoma—remains the only curative modality. Recently, several centers have explored the role of nephron-sparing surgery (partial nephrectomy) in selected patients. In general, the local recurrence rate after nephron-sparing surgery for T1 renal carcinoma is in the range of 2.7% to 5.8%, with a 90% disease-free survival rate at 5 and 10 years. These results are comparable to those obtained in similar patients treated with radical nephrectomy. The favorable results of nephron-sparing surgery do not extend to patients with > T1 lesions. Thus, patients with a solitary functioning kidney or other conditions that may affect future renal function can benefit from this procedure. Furthermore, the newer techniques of laparoscopic nephrectomy and cryoablation may offer similar surgical results with less blood loss, fewer days of hospitalization, and reduced narcotic requirements; these techniques are also an attractive alternative to open surgery for low-stage tumors. We agree with the authors' recommendation against routine nephrectomy in the setting of metastatic disease in the absence of symptoms. Although there is evidence that soluble tumor
products, including interleukin-6, macrophage colony-stimulating factor, interleukin-10, transforming growth factor-beta, and vascular endothelial growth factor, have negative effects on dendritic cells, elimination of the primary tumor has not conclusively been shown to reverse these deficits in a clinically meaningful way.

Certainly, nephrectomy following response to immune or other therapies, especially combined with resection of a solitary metastasis, can prolong disease-free survival in selected patients and should be considered. An ongoing Southwest Oncology Group study that is randomizing patients to nephrectomy or no surgery followed by interferon therapy will help further define the role of surgery in patients with metastatic renal carcinoma.

Chemotherapy
As noted by the authors, chemotherapy for metastatic renal carcinoma has been disappointing. This does not mean, however, that newer chemotherapeutic agents and other nonimmunologic approaches should be forever abandoned in cytokine-refractory patients.

Our recently completed phase II trial of gemcitabine (Gemzar) and continuous-infusion fluorouracil (5-FU) demonstrated a 17% response rate in a heavily pretreated cohort of metastatic renal carcinoma patients.[Rini BI, Vogelzang NJ, Dumas M, et al, unpublished data] Other trials using monotherapy with 5-FU or gemcitabine have produced response rates in the range of 5% to 10%, suggesting additive or synergistic effects of the combination.[5,6]

Clearly, new chemotherapeutic agents must continue to be developed. In addition, the hypervascularity that is typical of renal cancer may make the disease the ideal [proving ground] for the newer generation of angiogenesis inhibitors.

Immunotherapy
The authors review the major issues surrounding cytokine treatment for metastatic renal carcinoma. Interleukin-2 (IL-2 [Proleukin]) and interferon-alfa (Intron A, Roferon-A) are the mainstays of treatment, achieving responses rates ranging from 15% to 20%.

A recent Finnish trial demonstrated a survival advantage of interferon-alfa plus vinblastine over vinblastine alone.[7] Since only 2 of the 81 patients responded to vinblastine, while 16.5% responded to interferon, the trial provides strong evidence that cytokine treatment can improve overall survival compared to essentially no treatment.

Ritchie et al reported a similar survival advantage when treatment with 12 weeks of interferon-alfa was compared to 300 mg of daily medroxyprogesterone acetate in 335 patients with metastatic renal carcinoma.[8] Median survival was increased by 2.5 months in the interferon-treated group. The debate over high- vs low-dose IL-2 is ongoing. Current National Institutes of Health studies may demonstrate that high-dose IL-2 provides an advantage by increasing the percentage of durable complete responders. However, low-dose, subcutaneous, outpatient IL-2 regimens are an accepted option.

In an attempt to build on the partial success of cytokine therapy, investigators have studied many other immunologic approaches, including antibody and vaccine therapies (as outlined by the authors). Identification of renal carcinoma-specific antigens, as in melanoma, will facilitate the development of targeted approaches, including cluster of differentiation 8 (CD8+) T-cell-based therapy. A further understanding of dendritic cell function, T-cell activation, and costimulatory cytokines is also needed to develop effective approaches.

Finally, a novel immunologic approach to renal cell carcinoma has been developed involving the use of nonmyeloablative peripheral blood stem-cell transplantation. Immunosuppressive chemotherapy is followed by peripheral blood stem-cell infusion from a human lymphocyte antigen-matched sibling to induce a graft-vs-tumor effect. This approach has shown early promising results at the National Cancer Institute.[9]

Conclusions
The treatment of renal carcinoma often involves a coordinated effort by the surgeon, pathologist, and oncologist. The issues reviewed here highlight the current knowledge base and some promising new approaches. This challenging disease affords limitless research opportunities, and every avenue of antitumor therapy needs to be explored.

References:


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