Management of Renal Cell Carcinoma

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Surgical resection remains the cornerstone of management for localized renal cell carcinoma. No effective postsurgical adjuvant therapy has been established for

Introduction

Renal cell carcinoma has been characterized as the “internist’s tumor” based on the diversity of presenting symptoms. These range from microscopic hematuria to abdominal pain to an abdominal or flank mass. An estimated 30,000 new cases of renal cell carcinoma will occur in the United States in the year 2000, and approximately 12,000 people will die from this disease. The majority (75% to 85%) of tumors are of clear cell histologic type, with papillary, chromophobic, oncocytic, and collecting-duct tumors comprising the remainder.

Although the incidence of kidney cancer has increased by 43% since 1973 in the United States, the 5-year survival rate improved by approximately 9% between 1974 and 1994. This increase in survival may be attributable to a stage migration resulting from earlier diagnosis. The more frequent use of sensitive abdominal imaging modalities in recent years may have contributed to the greater number of tumors detected at an early stage; this includes incidental renal masses detected during evaluation for other medical conditions.

The major etiologic factors implicated in the development of renal cell carcinoma are cigarette smoking, obesity (especially in females), and hypertension. Recently, mutations of the von Hippel-Lindau (VHL) gene have been identified in large numbers of patients with both sporadic and familial forms of renal cell carcinoma. Evolving evidence suggests that the VHL gene acts as a tumor suppressor and that restoration of the wild-type gene product can inhibit growth of renal cell carcinoma cell lines. The altered form of this protein can also enhance expression of vascular endothelial growth factor, which may contribute to the progression of kidney cancer by promoting vascularization.

Surgery

Approximately 45% of patients present with disease localized to the kidney and undergo surgical resection. Radical nephrectomy, entailing resection of the affected kidney, perirenal fat, and ipsilateral adrenal gland, has been the benchmark procedure for managing localized kidney cancer. Recent investigations have questioned the need for adrenalectomy and lymph node dissections in patients without an obvious abnormality of the adrenal gland on computed tomography (CT). More conservative surgical approaches, such as a partial nephrectomy (nephron-sparing surgery), are reserved for those with an absent, abnormal, or at-risk contralateral kidney. Patients with a normal contralateral kidney and small (≤ 4 cm), polar primary lesions may also be candidates for nephron-sparing surgery.

More aggressive surgical treatment is considered for patients presenting with a tumor that has invaded the renal vein and inferior vena cava. When a careful radiologic evaluation does not detect metastatic disease, these patients should be referred to a center staffed by surgeons who are experienced in performing resections of tumors extending into these venous structures.

The likelihood that localized kidney cancer will be cured by surgical removal of the tumor depends on several prognostic factors. The most important of these is pathologic stage on presentation. Patients who have a small tumor that is confined within the renal capsule have a more favorable prognosis than do those whose tumor extends beyond the capsule, invades the renal vein, or involves the local lymph nodes.

There is no established role for adjuvant systemic therapy following resection in patients with localized kidney cancer. Several trials of adjuvant radiotherapy or immunotherapy with interferon-alpha (Intron A, Roferon-A) or experimental autologous vaccines have failed to show a significant advantage for these approaches in preventing recurrence. Ongoing trials of interleukin-2...
(IL-2 [Proleukin]) and new vaccine trials are evidence of the continued interest in identifying effective adjuvant therapy for patients at high risk of relapse.

**Resection in the Setting of Metastatic Disease?**
The routine resection of primary kidney tumors in the presence of metastatic disease is not recommended. Some investigators have advocated nephrectomy in the context of metastatic disease because of a theoretical immune suppression attributed to the primary tumor. According to this theory, removal of the primary tumor would allow for more effective immunologic therapy of metastatic disease.

No conclusive evidence of immunosuppression has yet to be associated specifically with primary renal tumors. In the absence of definitive evidence of such immunosuppression, an alternative approach is to attempt immunologic therapy before radical nephrectomy and perform surgery if a major clinical response is achieved.

**Treatment Approaches for Metastatic Disease**

The patient with metastatic renal cell carcinoma presents the clinician with the opportunity to individualize therapy based on the specific characteristics and natural history of disease in that person. Several factors warrant this individualization of therapy: the wide spectrum of aggressiveness of renal cell carcinoma, the somewhat capricious role of the immune system in the biology of the disease, and the general lack of effective chemotherapeutic agents.

**Treatment of Solitary Metastatic Lesions**
For a patient with a solitary site of metastasis, surgery is considered in selected instances. Solitary metastatic lesions to the brain are managed either by surgical resection or stereotactic radiation therapy. Symptomatic osseous lesions may be treated with palliative radiation therapy or surgery, if the lesions are in a weight-bearing bone.

**Cytotoxic Chemotherapy**
The use of standard cytotoxic chemotherapy in patients with renal cell carcinoma has produced relatively disappointing results. Yagoda and colleagues reviewed all phase I chemotherapy trials published between 1983 and 1993, and found an overall response rate of 6.8% in 83 trials involving a total of 4,542 patients.

The use of the fluorinated pyrimidines, floxuridine (FUDR) and fluorouracil has been reported to yield slightly higher response rates (13%). However, most of these are partial responses of short duration. The above studies indicate that kidney cancer cells are resistant to the known forms of cytotoxic chemotherapy.

The inherent resistance of kidney cancer cells to cytotoxic chemotherapy has been attributed, at least in part, to a high expression of the multidrug resistance gene product (P-glycoprotein). Several trials have investigated the combined use of agents that inhibit P-glycoprotein and chemotherapy. In one such trial, no improvement in the efficacy of vinblastine was noted when dexverapamil was used to reverse P-glycoprotein.

**Immunotherapy**
Immunologic therapy has assumed a predominant role in the treatment of metastatic kidney cancer, for several reasons. First, as described above, cytotoxic chemotherapy has shown little efficacy. In addition, several interesting observations concerning the natural history of the disease have led to the hypothesis that modulation of the immune system may help control renal cell carcinoma. These include the development of late relapses after nephrectomy, prolonged stabilization of metastatic disease without treatment, and rare spontaneous regressions.

**Interferons**
The interferons were discovered in the 1950s based on their ability to mediate antiviral activity. Subsequently, it was learned that this family of cyto-kines contains numerous members, with the interferon-alpha subclass alone being composed of at least 14 individual genes. Since their initial description, it has also been learned that interferons have antiproliferative and immunomodulatory activities. The antiproliferative effect may result from an inhibition of protein synthesis, which is also part of the antiviral effect.

**Interferon-alfa**
The availability of purified natural and subsequently recombinant forms of interferon-alfa led to numerous trials of this cytokine for the treatment of kidney cancer. Interferon-alfa is a pleiotropic cytokine that is produced by leukocytes and binds to the same receptor as interferon-beta. Although the exact mechanisms by which interferon-alfa regulates the growth of kidney cancer remain unknown, the most likely include a combination of direct antiproliferative and immune-modulating activities mediated through the induction of numerous
other genes. The multiple immunologic effects of interferon-alfa alone include induction of major histocompatibility complex antigen expression, as well as enhanced natural killer cell activity. A very recent report described the ability of interferon-alfa to augment expression of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of the tumor necrosis factor family thought to be involved in antitumor immune responses. Thus, the proposal to use interferons in the treatment of malignancies is biologically well grounded. In addition to its use in renal cell carcinoma (described below), interferon-alfa is employed in the adjuvant therapy of high-risk malignant melanoma, as well as in the treatment of chronic myelogenous leukemia, hairy cell leukemia, and follicular lymphoma.

Interferon-alfa has been tested in multiple clinical trials, including several phase III studies, in metastatic kidney cancer. A reproducible response rate of 10% to 15% has been observed with the use of daily doses ranging from 5 to 20 million units administered subcutaneously. Approximately 1% of treated patients achieve a complete response. Higher response rates (approaching 30%) have been observed in patients with prior nephrectomy and with metastases confined to the lung. Randomized trials have shown a modest increase in survival time (2 to 7 months) in patients who received interferon-alfa treatment.

The side effects of interferon-alfa are well known and include fatigue, fever, bone marrow suppression, elevation of hepatic enzymes, and neuropsychiatric changes. These toxicities are dose-related, and appropriate dose reduction can allow for continuation of therapy with a decrease in side effects. Attempts to combine interferon-alfa with chemotherapeutic agents, such as vinblastine, not only have failed to improve survival but also have resulted in additional toxicity. Interferon-gamma (Actimmune) has also undergone clinical study in renal cell carcinoma. Like interferon-alfa, interferon-gamma has antiviral, anti-proliferative, and immunomodulating capabilities. Interferon-gamma differs from interferons-alfa and -beta with respect its cellular source, a distinct receptor system, and its spectrum of immunomodulating activities. Interferon-gamma is produced mainly by T-cells and natural killer cells and has significant effects on macrophage activation and cytotoxic T-cell responses.

Phase I and II data trials suggested a 15% to 30% response rate of renal cell carcinoma to interferon-gamma. Subsequently, a well-designed and well-conducted, randomized, placebo-controlled, phase III trial, conducted by the Canadian Urologic Oncology Group, showed that interferon-gamma has no significant effect on response rate, time to progression, or median survival, as compared with placebo.

**Interleukin-2**

Interleukin-2 is a cytokine that is thought to exert its major antitumor effect through lymphocyte activation. An antiproliferative effect has not been demonstrated. Initial studies of IL-2 at the National Cancer Institute (NCI) indicated a relatively high response rate (30%) in patients with renal cell carcinoma. Subsequent studies demonstrated a 15% response rate, with approximately 3% to 5% representing complete responses and some appearing to be durable. Large bolus doses of IL-2 are associated with the capillary leak syndrome and require vigilant inpatient monitoring. Also, any regimen that includes high-dose IL-2 should be administered at a facility where the staff is experienced in dealing with the toxicities of this agent. Interleukin-2 has been administered at varying doses and via different routes in an attempt to mitigate significant and sometimes life-threatening toxicities. Trials employing lower doses of intravenous therapy, as well as outpatient use of subcutaneous IL-2, suggest that the overall response rate is not affected by a decrease in dose or a change in route of administration. The durability of responses obtained with lower doses of IL-2 is currently being investigated.

**Combination Cytokine Therapy**

As a logical follow-up to the above results demonstrating modest but reproducible efficacy of IL-2 and interferon-alfa, several groups have conducted clinical trials to investigate the combination of the two cytokines. The results of one study indicate that although the combination of IL-2 and interferon-alfa yields a higher response rate than either IL-2 or interferon-alfa alone (18.6% vs 6.5% vs 7.5%), survival rates are not significantly different and toxicity is greater with the combination. Thus, combination cytokine therapy has not yet been shown to result in a survival benefit compared to monotherapy.

**Monoclonal Antibody Therapy**

The G250 monoclonal antibody has been the subject of investigation in kidney cancer for many years. This monoclonal antibody recognizes an antigen present on the majority of renal cell carcinomas. Although the target of G250 is also found on biliary ducts, radiolocalization studies have shown that a small unlabeled dose of G250 administered before a large labeled dose can effectively
saturate binding sites in the biliary tree without affecting binding to the kidney cancer. With the development of chimeric G250 to minimize human antimouse responses, this agent represents a logical choice for further development as a passive immunotherapeutic agent for renal cell carcinoma.

It has also been found that some renal cell carcinomas overexpress the HER-2/neu protein. Her-2/neu is a member of the epidermal growth factor receptor family, which has been implicated in the pathogenesis of some breast cancers through enhanced activation of an autocrine growth loop. Trastuzumab (Herceptin) is a humanized monoclonal antibody that targets HER-2/neu overexpressing cells, as well as blocks signaling through the receptor tyrosine kinase. Thus, it is envisioned as both an antiproliferative and an immunologic therapy. Once more information is obtained regarding the proportion of kidney cancers that overexpress HER-2, trastuzumab can be considered for clinical trials in this disease.

**Tumor Vaccines**

The use of tumor vaccines represents another immunologic approach to the treatment of renal cell carcinoma. Modified autologous tumor vaccines have been studied most extensively. A randomized trial found that postsurgical (adjuvant) use of an autologous tumor vaccine containing bacillus Calmette-Guérin (BCG) did not decrease the rate of recurrence.

A further modification of the autologous vaccine approach has used tumor cells transduced with a retroviral vector containing granulocyte-macrophage colony-stimulating factor (GM-CSF). In a trial comparing vaccine containing GM-CSF with standard nontransduced vaccines, a more intense inflammatory infiltrate was seen at vaccination sites in patients receiving the GM-CSF-transduced vaccine. The question of whether this immunologic finding will translate into clinical benefit requires additional trials.

An additional approach to the autologous vaccine system has been to use autologous tumor cell lysate to pulse dendritic cells ex vivo. The antigen-loaded dendritic cells are then injected back into the patient, and immunologic and clinical responses can be monitored.

**Possible Vaccine Targets**

Based on advances in basic immunology made during the past 10 years, it may now be possible to identify specific antigens that can be recognized by the immune system. Through the use of the SEREX technique (screening of cDNA expression libraries derived from human tumors with autologous antibody) and the identification of peptides bound by individual patients' major histocompatibility complex molecules, new targets for humoral and T-cell responses, respectively, can be found. With this information, vaccines can be designed to present such antigens to the appropriate arm(s) of the immune system. Similar approaches have been used to identify antigens and design peptide vaccines for melanoma, based on an analysis of individual patients' T-cells.

Possible targets for new vaccines for kidney cancer include prostate-specific membrane antigen (PSMA), MAGE-3, and HER-2/neu (Table 1). Prostatic-specific membrane antigen is a cell surface protein found on normal and malignant prostate epithelium that possesses folate hydrolase activity. It has recently been shown to be expressed on the tumor vasculature of many solid tumors, including renal cell carcinoma. Given the highly vascular nature of kidney cancers, targeting the tumor vasculature with a PSMA vaccine is an attractive new treatment approach.

MAGE-3 is a so-called cancer-testis antigen that is expressed mainly on tumors and normal testes. It was originally identified as a target of immune recognition for T-cells in melanoma patients, and clinical trials of MAGE peptide vaccines in melanoma patients have already begun. More recent investigations have shown that MAGE-3 is expressed in a high percentage of kidney cancer tumor samples and cell lines.

As described previously, renal cell carcinomas have been shown to overexpress HER-2/neu. This observation provides a rationale for the use of trastuzumab for the treatment of the disease and/or the development of vaccines to specifically target this antigen.

As mentioned earlier, mutations in the VHL gene are associated with the development of both sporadic and familial renal cell carcinoma. It is possible that some of the mutations in this gene may create attractive epitopes for the design of novel tumor vaccines. A similar strategy has been used with an epitope created by mutated p53 in experimental murine sarcoma.

**Summary**

Despite extensive investigations with many different treatment modalities, metastatic renal cell carcinoma remains highly resistant to systemic therapy. Immunologic therapy with cytokines, such as interferon-alfa and IL-2, benefit relatively small numbers of patients. Conventional chemotherapy,
alone or in combination with cytokines, is of very little use. Small numbers of patients exhibit complete or partial responses to interferon and/or interleukin-2, but most patients do not respond and few survive over the long term. Preclinical studies aimed at recognizing new potential antigens present on kidney cancer cells and clinical investigations directed toward identifying new agents and treatment programs that demonstrate improved antitumor activity against metastases remain the highest research priorities. New immunologic approaches to the treatment of both advanced and high-risk postsurgical disease are focusing on novel vaccine therapies that target both renal epithelial and vascular antigens.

References:

Suggested Readings


