Introduction

Approximately 31,000 new cases of renal cell cancer are diagnosed annually in the United States, and the disease is responsible for an estimated 12,000 deaths each year.[1] One third of the patients present with metastatic disease and 30% to 40% of the remainder will eventually develop distal metastases.[2] The median survival of patients with metastases is only eight months, with a five-year survival rate of less than 10%.[3]

Surgery is the standard treatment for localized disease. In metastatic disease, the role of surgery is limited to palliation of symptoms related to the primary tumor, to treatment of patients selected for experimental protocols, or to individuals with few resectable metastases. Chemotherapy, radiation therapy, and hormonal treatments also are ineffective.[3]

Many anecdotal cases describing spontaneous regression of metastases following nephrectomy led to the belief that the patients mounted an immune response against the tumor. However, a critical review by Montie et al[4] could validate spontaneous regression in less than 1% of patients treated by nephrectomy. Nevertheless, these observations led to the assumption that enhancement of the immune response against the host tumor can overcome the malignancy. This approach is defined as immunotherapy and uses a variety of biological response modifiers and activated immune cells.

Interferons

Initial attempts to treat renal cell cancer with immunotherapy used interferons as biological response modifiers. Interferons are glycoproteins produced by mammalian cells in response to viral infections or other inducers. Three major classes of interferons have been characterized. Interferon alpha (IFN-alpha) is produced by leukocytes; interferon beta (IFN-beta) is produced by fibroblasts, lymphoblastoid cells, macrophages, and epithelial cells; and interferon gamma (IFN-gamma) is produced by activated lymphocytes. Interferons have antitumor properties, which may be mediated through a direct cytotoxic effect on tumor cells or through augmentation of the immunogenicity of tumors by upregulation of histocompatibility and tumor-associated antigens, and/or activation of macrophages, T lymphocytes, and natural killer cells.

IFN-alpha is one of the first biologic agents to yield promising results in the treatment of renal cell cancer. Analysis of phase I and II trials of IFN-alpha in the literature suggests an overall objective response rate of approximately 17%. However, response rates have been as high as 29%, including rare complete responses.[5] Several clinical trials combining IFN-alpha with chemotherapeutic agents such as cyclophosphamide, doxorubicin, fluorouracil (FU), cisplatin, mitomycin C, or vinblastine have not shown a combination more effective than IFN-alpha alone. However, the toxicity of these regimens increased.[6-8]

The results of IFN-gamma alone have been highly variable, but when sequentially administered with IFN-alpha, objective response rates of 27% have been observed. Otherwise, IFN-gamma has not had a major impact in this disease.[9,10]

Interleukin-2 Immunotherapy

In 1992, the Food and Drug Administration approved the use of IL-2 for the treatment of metastatic renal cell cancer. IL-2 is a 15,000 dalton glycoprotein secreted by activated T lymphocytes, which can be produced in large quantities by recombinant DNA technology. IL-2 is a potent growth factor that causes T-cell proliferation and differentiation, enhances natural killer-cell function, and can mediate the regression of cancer in experimental animals and selected patients. Lymphokine-activated killer (LAK) cells are generated by incubation of human peripheral-blood lymphocytes for three to four days in the presence of IL-2. LAK cells are activated lymphocytes capable of lysing a variety of fresh tumor cells and cell lines. In animal models, the combination of IL-2 and adoptively transferred LAK cells has been more effective than IL-2 alone in the eradication of metastases.[11]

The first clinical trials[12,13] with IL-2 alone or in combination with LAK cells were initiated in 1984 for the treatment of different types of metastatic cancers. The best responses were observed in patients with metastatic melanoma and renal cell cancer. Reports summarizing the trials in the 1980s[12,13] showed four complete and eight partial responses in 54 patients with metastatic renal cell cancer treated with high-dose IL-2 (22% response). Eight complete and 17 partial responses were seen in 72 patients who received IL-2 plus LAK cell therapy (35% response). Many of the responses were sustained, with 10 responses lasting more than two years. The median response duration was 14 months. Although the overall response appeared to be comparable among the two groups, patients who received IL-2/LAK cell therapy had a higher rate of complete response. These data are comparable to those recently reported in a prospective, randomized trial of high-dose IL-2 alone or in conjunction with LAK cells for the treatment of patients with renal cell cancer.[14] Complete responses were observed in seven (14%) of 49 patients treated with LAK plus IL-2 and in four (8%) of 48 patients treated with IL-2 alone. In a follow-up of more than five years, no difference in survival was seen in patients in the two treatment groups.[14] Tumor regression was seen in lung, liver, bone, subcutaneous tissues, and other sites but, in general, the best responses were observed in
Immunotherapy of metastatic kidney cancer in early trials suggested that better responses to immunotherapy were observed in patients who had resection of the primary tumor prior to therapy. However, many patients who have a nephrectomy in preparation for immunotherapy cannot be so treated due to complications of the surgery or progression of the tumor during the recovery period.[15] Patients who receive immunotherapy following nephrectomy tolerate similar doses of IL-2-based therapy, experience comparable toxicities, and demonstrate similar response rates as patients with their tumor-bearing kidney in situ.[16] However, while patients treated with their kidneys in place may respond in extrarenal sites of metastasis, an objective response is less likely in the primary tumor. Prospective, randomized trials are needed to settle the issue of the timing for nephrectomy in immunotherapy protocols.

IL-2 therapy is associated with significant toxicity that is dose-dependent and more severe with high doses. IL-2 toxicity is manifested by a vascular leak syndrome as a result of increased capillary permeability. This leads to fluid retention, interstitial edema, hypotension, decreased peripheral vascular resistance, an increase in cardiac index, tachycardia, and oliguria.[17]

Pulmonary edema, another manifestation of the vascular leak syndrome, can lead to respiratory failure, and 5% to 10% of patients receiving high-dose IL-2 therapy require pulmonary intubation and mechanical ventilation.[17] Renal complications observed with IL-2 therapy appear to be the consequence of prerenal azotemia and are fully reversible following termination of therapy. Preexistent impairment of renal function, however, increases the likelihood and prolongs the course of renal failure. Common gastrointestinal toxicities include nausea, vomiting, diarrhea, anorexia, and stomatitis. Gastrointestinal hemorrhage, bowel infarction or perforation, and acute pancreatitis are less common. Endocrine and metabolic toxicities, dermatologic complications (pruritus, rash), neurotoxicity (mental status changes, agitation, disorientation, hallucinations, seizures, transient ischemic attacks, cerebrovascular accidents, coma), hematologic toxicity, fever and chills, sepsis, and many other toxicities of varying frequency have resulted in the interruption or discontinuation of therapy.[17]

Although IL-2 toxic side effects are reversible following termination of treatment, patients should have normal cardiac, pulmonary, hepatic, cerebral, and renal functions documented prior to treatment. Careful monitoring during treatment is essential, and adequate organ perfusion must be maintained. This intensive therapy requires a dedicated approach.

Alternate regimens of IL-2 administration were used to diminish IL-2 toxicity. Sosman et al.[18] developed a less toxic regimen consisting of four repetitive weekly cycles of four days of low-dose IL-2 administered by continuous intravenous infusion. Using this regimen, partial responses were observed in three (18%) of 17 patients with renal cell carcinoma. The addition of LAK cells to this regimen failed to show an advantage. A recent multicenter phase II trial[19] of continuous-infusion IL-2 in 45 patients with advanced renal cell carcinoma showed a response rate of 13%. Antitumor responses were observed using subcutaneous[20,21] or inhalational[22] administration of IL-2. Although these modes of administration are less toxic and may be administered on an outpatient basis, their efficacy is no greater than that of high-dose IL-2. In a recent report,[23] high-dose intravenous IL-2 (720,000 IU/kg) every eight hours was compared with low-dose intravenous IL-2 (72,000 IU/kg) administered according to a similar schedule. The low-dose regimen had similar efficacy but less toxicity.

Tumor-Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes (TILs) are lymphoid cells isolated from solid tumors. When cultured in the presence of IL-2, TILs can be activated and expanded in great numbers. In animal immunotherapy models, TILs are 50 to 100 times more effective than LAK cells on a cell-to-cell basis.[24]

TILs can be prepared from primary or metastatic tumors. The specimens are excised and digested in an enzyme solution, and the sterile, single-cell suspension is incubated in the presence of IL-2. In three to four weeks, an activated T-lymphocyte population is generated, and approximately 1011 cells are reinfused into the patient together with IL-2. The lymphocyte subpopulations vary according to the histology of the original tumor, culture conditions, IL-2 concentration, and other variables. The TIL phenotype does not appear to correlate with the antitumor responses observed in clinical trials. TILs from melanomas often demonstrate in vitro specificity for the autologous tumor in terms of either cytotoxicity or specific cytokine release. However, this has generally not been observed with TILs from renal cancer. The majority of the clinical data regarding TIL therapy comes from melanoma studies[25] in which significant responses have been demonstrated. Some of these studies show that TILs circulate in patients for extended periods of time and that they selectively migrate to the tumor and sites of metastases.

Responses to TIL therapy in patients with renal cell carcinoma have been less frequent and have shown minimal clinical benefit. More recently, however, Beldegrun et al.[26] and Figlin combined cytokine-primed TIL or a specifically selected subpopulation of TIL (CD8+ T cells) with IFN-alpha and low-dose IL-2 and saw 30% and 41% response rates, with 15 and 41 months median survival, respectively (R. A. Figlin, personal communication, 1996). These encouraging results have led to a promising multi-institutional trial comparing IL-2 alone vs IL-2 with CD8-selected TIL cells in patients with metastatic renal cell cancer.

Combined Immuno-therapy Regimens

The combination of IL-2 with various biologic response modifiers, including IFNs, TNF-alpha, and tumor specific monoclonal antibodies, demonstrated a synergistic or additive therapeutic effect in animal models and led to the initiation of clinical trials using this approach.[27] At the present time, the most noteworthy results involve outpatient regimens of IL-2 plus IFN-alpha with or without chemotherapy agents such as FU, which resulted in higher response rates for patients with metastatic renal cell carcinoma.

Since early reports by Atzpodien et al.[28] and Figlin et al.[29] of 30% and 25% response rates to IL-2 plus IFN-alpha, several other studies reproduced these promising results in larger population of patients with renal cancer. Lumen et al.[30] recently noted 23% response rates with subcutaneously administered IL-2 plus IFN-alpha. Hanninen et al.[31] reported an overall response of 28% in 79 patients treated with an outpatient regimen of subcutaneous IL-2 plus IFN-alpha. In the same study, a greater response rate of 39% and a lower grade of toxicity were obtained in the treatment of 120 patients using the combination of subcutaneous IL-2, IFN-alpha, and intravenous FU, suggesting that this chemoimmunotherapy regimen could be superior to immunotherapy alone for the treatment of metastatic renal cell cancer.
Cytokine Gene Therapy

The various immunotherapeutic approaches used in the clinical trials described previously show that systemic administration of cytokines can induce regression of primary and metastatic tumors in selected patients but with significant toxicity. The belief that cytokines could demonstrate increased antitumor efficacy and reduced toxicity if delivered directly at the tumor site has led to a new approach of gene therapy for neoplastic diseases. Cytokine gene therapy is based on the use of recently developed recombinant DNA technology and sophisticated molecular techniques to insert cytokine genes either in TILs or in autologous tumor cells. Pioneer studies conducted by Rosenberg et al.[35] demonstrated the safety of genetically altered cells for human therapy using retroviral-mediated neomycin-resistant gene transduction into TILs. Those studies also showed that transduced TILs localize and persist in metastatic sites of melanoma patients. In renal cancer, IL-2 and/or IFN-alpha gene retroviral transduction of autologous tumor cell lines or TIL isolated from renal tumor specimens were successful in vitro and showed activity.[36,37] Although promising, the gene therapy approach is still in early stages of development, and crucial basic issues (e.g., gene delivery systems, frequency of transduction, and gene expression) are undergoing extensive investigation. Several clinical trials using this approach are underway, but only limited localized responses have been observed thus far. Another complementary modality may be necessary to enhance the effects of gene therapy.

Future Prospects

Metastatic renal cell cancer has been more responsive to immunotherapy than to conventional therapies, even though limited response rates of 10% to 30% have been obtained with various immunotherapy approaches. Clinical trials using high-dose intravenous IL-2 treatment for selected patients have shown that this protocol is superior to low doses but requires intensive care due to severe toxicity. IL-2 also can be administered subcutaneously on an outpatient basis since it results in decreased and manageable toxicity. However, its efficacy is limited unless combined with additional agents. Randomized trials of high-dose IL-2 combined with LAK cell therapy showed a greater overall response rate but no advantage in patient survival. Of the different combinations of cytokines tested in clinical trials, IL-2 combined with IFN-alpha resulted in better response rates than either cytokine alone when administered subcutaneously. Recent regimens combining subcutaneous administration of IL-2 and IFN-alpha with FU on an outpatient basis need further evaluation. Additional trials using IL-1, IL-4, IL-6, granulocyte-macrophage colony-stimulating factor, cytokines, or the combination of IL-2 with anti-CD3 monoclonal antibodies showed no antitumor responses. A recently discovered immunoregulatory cytokine, IL-12, has been successful at complete eradication of murine tumors and has shown enhanced antitumor activity when combined with IL-2 in murine renal tumors.[38] Clinical trials are underway to test IL-12.

Further studies on different combinations of immunotherapy with other modalities (e.g., chemotherapy, radiation, surgery, and gene therapy) could yield increased response rates or safer and more practical treatments for patients with renal cell cancer. However, phase III trials comparing these regimens with high-dose IL-2 regimens will be required to determine superiority.

References


