Immunotherapy for Renal Cell Carcinoma

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THE AMERICAN CANCER SOCIETY estimates that more than 25,000 new cases of renal cell carcinoma will be diagnosed in the United States in 1991 and that more than 10,000 deaths will be attributed directly to the disease.[1] Surgical extirpation for localized disease remains the only curative therapy, while traditional treatment of disseminated disease (chemotherapy and radiotherapy) is ineffective.

In the past decade, advances in immunology and molecular biology have opened the way for promising new treatment modalities of metastatic renal cell carcinoma. These approaches use the cytokines interferon (IFN) and interleukin-2 (IL-2), alone or in combination, or cells from the patient's own immune system expanded ex vivo by IL-2 to treat the metastatic lesions. An even newer approach uses "gene therapy" to modify cells from the immune system or to modify the tumor itself into acting as a "vaccine." This report presents a brief overview of these new treatment modalities.

SINGLE-AGENT THERAPY

IFNs are naturally occurring proteins elaborated by cells in response to antigenic stimulation, either by viruses or by malignant cells.[2] With the advent of recombinant DNA technology, large quantities of IFN have been available for laboratory and clinical investigations. IFN has been used as monotherapy in more than 1,000 patients with renal cell carcinoma in multiple clinical trials, with an overall objective response rate of 13%.[3] These trials have used various doses, schedules, and administrative routes. At the University of California at Los Angeles (UCLA), 99 patients with metastatic renal cell carcinoma have been treated with IFN-α monotherapy, with an objective response rate of 16% (2 complete responses and 13 partial responses).[4] Responses appear to correlate with previous nephrectomy, good performance status, a long disease-free interval, and lung-predominant disease. The median duration of response averages 6 to 10 months with few durable complete remissions. Toxicity secondary to IFN therapy includes flu-like symptoms, fatigue, and gastrointestinal upset, with resolution of toxicity occurring shortly after discontinuation of therapy.

IL-2 is a lymphokine produced and secreted by T lymphocytes and involved in virtually all immune responses in which T cells play a role.[5] IL-2 has shown antitumor effects in animal models.[6] In vitro studies demonstrated that lymphocytes exposed to IL-2 developed the ability to kill fresh tumor cells but not fresh normal cells.[7] These cells were referred to as lymphokine-activated killer (LAK) cells. Numerous clinical trials have evaluated IL-2 as monotherapy for metastatic renal cell carcinoma. The predominant regimen has been IL-2 on an intravenous (IV) bolus schedule and has shown an overall response rate of 17.8%. Responses were durable in most patients, with the longest continuing at 34 months. IL-2 has also been used on a continuous-infusion schedule with overall response rates of 13% to 19%.[8] There is no evidence from these trials that continuous-infusion IL-2 is either more active or less toxic than the high-dose bolus schedule of administration.

The toxicity of IL-2 has been well documented and includes fevers, chills, malaise, nausea, vomiting, diarrhea, and other constitutional symptoms. Renal dysfunction and cardiopulmonary embarrassment are the most frequent serious side effects. IL-2 therapy is associated with a vascular leak syndrome which can progress to hypotension, fluid retention, respiratory distress and failure, prerenal azotemia with oliguria and low fractional sodium excretion. Cessation of IL-2 therapy results in reversal of side effects and rapid

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recovery. Renal function returns to baseline values within 7 days in 62% of patients and within 30 days in 95% of patients.[9,10] Treatment-related mortality is less than 2%.

COMBINATION BIOLOGIC THERAPY

The modest success of cytokine monotherapy has stimulated interest in therapy with combinations of agents. These combinations have shown direct antitumor effects in vitro that are both additive and synergistic. It is thought that IFN therapy may enhance expression of class I major histocompatibility complex (MHC) antigens, thus augmenting their immunogenicity. This effect may then increase the tumor's susceptibility to attack by IL-2 activated lymphocytes. Preclinical animal studies have documented the in vivo therapeutic synergy between IFN-α and IL-2.[11,12] Several trials of IL-2 and IFN-α therapy in patients with metastatic renal cell carcinoma have been instituted. Rosenberg et al reported a 31% overall response rate, including 4 complete responses, in 35 patients.[13] A National Cancer Institute–sponsored extramural phase II study of IL-2 and IFN-α was conducted based on this previous study; however, response rates of only 12.5% were attained.[14] These trials used IV bolus administration of each cytokine, and toxicity was similar to that seen in trials of IL-2 alone.

At UCLA to date we have treated 38 patients with renal cell carcinoma on a protocol of continuous-infusion IL-2 and subcutaneous IFN-α. Only the first 4 days of treatment are administered on an inpatient basis. Each 4-week treatment period (one course) is followed by a 2-week rest. The 4-week course is repeated until disease progression, unacceptable toxicity, or a maximum of 6 courses. Median patient age is 57 years (range, 29 to 70 years). Most patients had undergone previous nephrectomy. Metastatic sites included lymph nodes, bone, and liver but were predominantly pulmonary. Significant toxicity (grade IV) occurred in only 10% of patients. An overall response rate of 29% (11 patients) has been observed. The median duration of responses has not yet been reached at 19 months. The median time to response was 11 weeks. Two partial responders whose sites of metastatic disease were renal fossa and mediastinal lymph nodes, respectively, were found to have a pathological complete remission (pCR) following surgery. A third patient had a pCR of the axillary nodes, and a surgical complete remission was achieved with salvage nephrectomy. Median survival of patients obtaining a partial remission has not been reached with a median follow-up time of more than 19 months.

More recently, combination therapy studies using subcutaneous IL-2 and IFN-α have been performed on an outpatient basis, with minimal toxicity. Atzpodien et al reported a 29% overall response rate in 34 patients.[15] The duration of response in patients with complete remissions exceeded 19 months. Sznol et al, using a different regimen of the same combination therapy, achieved a 22% response rate in 23 patients.[16] It seems that combination cytokine therapy can be safely administered in an outpatient setting; however, larger-scale trials are needed to confirm the efficacy of the treatment.

ADOPTIVE IMMUNOTHERAPY

Adoptive, or passive, immunotherapy involves the transfer of active immunologic reagents to the tumor-bearing host. These reagents can be cells with antitumor reactivity that can directly or indirectly mediate antitumor effects. The antitumor cells are sensitized either nonspecifically, as in LAK cells, or specifically to tumor antigens, as in tumor-infiltrating lymphocytes (TILs).

In 1985, Rosenberg et al reported the initial NCI results of adoptive immunotherapy with LAK cells and IL-2 in 25 patients with advanced cancer. This study was then extended to include 139 patients by 1988, 54 of whom had renal cell carcinoma.[17] Of these 54 patients, 7 experienced complete responses and 10 had partial responses, for an overall response rate of 33%. These results contrasted with an 18% response rate for 38 patients with renal cell carcinoma treated with high-dose bolus IL-2 alone. Fisher et al reported the results of an extramural NCI phase II study.[18] A 16% objective response in 35 patients was achieved. The combined response rate of all published trials administering IV bolus IL-2 every 8 hours with LAK cells is 23.5%, as summarized by Sznol.[8] He concludes that the data do not support a major contribution by LAK cells to the efficacy of high-dose bolus IL-2 in patients with renal cell carcinoma.

A more recent alternative adoptive immunotherapy modality for renal cell carcinoma has been the addition of TILs to IL-2 to IL-2 and IFN-α. TILs are predominantly T cells that can be isolated from solid tumors when single-cell suspensions are cultured in the presence of IL-2.[19-21] Unlike LAK cells, TILs can be expanded in large numbers and maintained in long-term cultures. More significantly, the therapeutic potency of TILs is 100 times greater than that of LAK cells on a cell-to-cell basis.[22] Adoptively transfused TILs have been shown to have long-term survival in murine studies.[23] In addition, clinical trials have shown that TILs will localize preferentially to metastatic deposits in patients with malignant melanoma.[24,25] Rosenberg et al reported one complete response and 10 partial responses in trials involving 20 patients with metastatic melanoma.[26] The complete response had a duration of 13 months, whereas the partial responses had a 2- to 9-month duration. The results of these studies prompted initiation of clinical trials of TIL in patients with metastatic renal cell carcinoma.

Because the initiation of TIL culture requires the procurement of fresh tumor tissue, patients must first undergo either a nephrectomy or resection of a metastatic lesion. We have previously described our method for the generation and expansion of TILs from fresh human renal cell carcinoma.[27] Cell cultures produce TILs, which can then be expanded in IL-2–containing medium, so that the total lymphocyte count increases more than 65,000-fold. Phenotypic analysis shows that the majority of the TILs are cytotoxic/suppressor cells. In addition, these cells can be subdivided on the basis of their lymphokine-secretion profiles, which may allow for selecting subsets with greater antitumor efficacy.[28]

A phase I trial of TIL therapy of renal cell carcinoma has been instituted at UCLA.[29] Efforts to improve the efficacy of this modality involve in vivo priming by lymphokines before nephrectomy and then infusion of the primed TILs in combination with IL-2 and IFN-α. Of 10 patients treated with this method, 2 have achieved ongoing complete clinical responses with duration greater than 18 months. Tumor regression is generally seen within 6 weeks of initiation of therapy. The toxicity of TIL therapy is predominantly secondary to IL-2 infusion. There have been no treatment-related deaths.

GENE THERAPY

The ability to introduce and express foreign genes in cells has raised hopes that this technology may be applied to clinical oncology. It is possible that genes could be introduced into TILs, which might code for cytokines and would be produced in proximity to the tumor, thereby increasing the potential for antitumor efficacy. The feasibility and safety of using retroviral-mediated gene transfer in humans has already been demonstrated.[30] Current studies are underway attempting to incorporate genes coding for tumor necrosis factor into TILs and to use these modified cells in clinical trials.[31] Future studies will evaluate the feasibility of inserting genes for other cytokines.

Another approach evolving from this technology uses genetically modified tumor cells as a vaccine. Experiments have shown that insertion of the gene for class I MHC antigens into tumor cells increases their immunogenicity. These cells then stimulate the production of host TILs that would otherwise not be produced because of low immunogenicity.[32]

THE ROLE OF NEPHRECTOMY IN METASTATIC DISEASE

An issue that has yet to be resolved is the role of nephrectomy in patients with metastatic renal cell carcinoma who are being entered into clinical immunotherapy trials. The literature contains little objective evidence on the impact of previous nephrectomy in IL-2–based therapy.[33] It may be that tumor burden is an important factor in response to immunotherapy, and nephrectomy would be necessary for "debulking." Moreover, metastatic lesions are more likely to respond than the primary tumor. Salvage nephrectomy would be justified in situations in which the primary tumor is the only persistent focus of cancer. Finally, histopathologic examination of the tumor would give valuable information on the effect and mechanism of immunotherapeutic modalities. At UCLA, two patients treated with IL-2 and IFN-α became free of distant metastatic disease while the primary tumor was in situ. Nephrectomy resulted in a surgical complete response. Kim et al reported preliminary data suggesting that surgical

resection of residual tumor following partial response to IL-2 treatment may significantly prolong response.[34] Certainly, additional evaluation is necessary before defining the exact role of nephrectomy as an adjunct to immunotherapy for metastatic disease.

SUMMARY

The prognosis for patients with metastatic renal cell carcinoma may be brightening. Immunotherapy may offer an effective alternative approach for this disease. Continuing advances in immunology and molecular biology will probably reinforce the early enthusiasm for this method. Although still investigational, cytokine monotherapy and combination therapy, adoptive immunotherapy, and gene therapy appear to be promising therapeutic modalities for selected patients with metastatic renal cell carcinoma.

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