Immunotherapy for metastatic renal-cell carcinoma

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Summary. The treatment of metastatic renal-cell carcinoma remains a major challenge. Immunotherapy is a new approach to the treatment of advanced cancer and might offer a window of hope to patients with renal-cell carcinoma. The enthusiasm for this form of cancer therapy is mainly due to the recent advances achieved in immunology and molecular biology. This report reviews our experience with immunotherapy for renal-cell carcinoma. Although it is yet experimental, adoptive immunotherapy and combined cytokine administration appears to be a promising therapeutic modality for a selected group of patients with advanced renal-cell carcinoma.

Renal-cell carcinoma accounts for approximately 3% of adult cancers. The American Cancer Society estimates that approximately 25,300 new cases of renal-cell carcinoma will be diagnosed in the United States in 1991, with approximately 10,600 deaths being directly attributable to this disease [1]. Neither chemotherapy nor radiation therapy have shown to be effective against metastatic renal-cell carcinoma [2].

Recently, new and promising modalities of immunotherapy have gained prominence in clinical trials treating renal-cell carcinoma. Patients were given the lymphokine interleukin-2 (IL-2) either alone or in combination with other lymphokines such as interferon (IFN)-alpha so as to activate their immune system against the cancer. Alternatively, lymphokines were given in combination with activated killer cells that had been derived from the peripheral blood, designed lymphokine activated killer (LAK) cells, or directly from the tumor, designated tumor-infiltrating lymphocytes (TILs) [3].

Combination biologic therapy

The ability of the immune system to mediate antitumor effects depends on a series of immunologic signals; thus, it is plausible that treatment with a combination of lymphokines may prove to be beneficial for cancer patients, particularly those with renal-cell carcinoma. Combinations of cytokines have shown direct antitumor effects in vitro that are both additive and synergistic. Furthermore, interferon treatment may augment the immunogenicity of tumor cells by enhancing their expression of class I major histocompatibility complex (MHC), making them more susceptible to killing by IL-2-activated lymphocytes. In several experimental animal models, substantial in vivo therapeutic synergy has been demonstrated following treatments with both IL-2 and interferon-alpha (IFN-alpha) as compared with either agent alone [4, 5]. Several studies reported in the literature [6-8] have used IL-2 and IFN-alpha in patients with advanced renal-cell carcinoma. These trials involved different routes of administration (i.v. infusion vs s.c.), schedules (continuous infusion vs bolus), and different doses of each cytokine. The results suggested an objective response rate of 25% - 35% for combination therapy in patients with metastatic renal-cell carcinoma.

To date, 30 patients with measurable renal-cell carcinoma have been treated at UCLA with rIL-2 (2 milliunits/m²) given by continuous i.v. infusion on days 1 - 4 and with Roferon-A (6 milliunits/m²) given i.m. or s.c. on days 1 and 4 of each treatment week. Only the first 4 days of treatment were carried out on an inpatient basis. Each 4-week treatment period (1 course) was followed by a 2-week rest. A 4-week course was repeated either until disease progression or unacceptable toxicity became evident or for a maximum of six courses. The median age of the subjects was 57 years (range, 29 - 70 years), and there were 25 men and 5 women. In all, 23 (76%) patients had undergone a prior nephrectomy. Metastatic sites included the lungs (73%), lymph nodes (23%), local sites (13%), bone (13%), liver (13%), and other (20%). Grade IV toxicity occurred in 3 subjects (10%). In all, 1 complete clinical response (3.3%) and 8 partial clinical responses (27%) were observed, for a total response rate of 30%. Two subjects showed a surgical complete response following a salvage nephrectomy. Three patients

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achieved pathologically confirmed complete remissions following partial clinical remissions in peripheral and mediastinal lymph nodes and recurrent renal fossa mass, respectively. All of the pathologically complete remissions are ongoing.

Adoptive immunotherapy

Adoptive (passive) immunotherapy involves the transfer to the tumor-bearing host of active immunologic reagents, such as cells with antitumor reactivity, that can either directly or indirectly mediate antitumor effects. Autologous circulating lymphocytes obtained by leukopheresis of the patient were activated and expanded in IL-2 in vitro leading to the generation of LAK cells. These LAK cells were then reinfused into the patients in combination with IL-2 [9-11].

In 1985, Rosenberg et al. [12] reported the initial National Cancer Institute (NCI) results of adoptive cellular therapy with LAK cells plus IL-2 in 25 patients with advanced cancer and then extended the study to include 139 subjects by 1988. Among 54 treated cases of renal-cell carcinoma, 7 patients achieved a complete response and 10 showed a partial response, for a total response rate of 33%. Among 38 patients with renal-cell carcinoma who were given a high-dose bolus of IL-2 alone, 4 complete responses and 3 partial responses were achieved, for a total response rate of 18.4%. The responses occurred at a number of different sites, including the lung, liver, soft tissue, subcutaneous tissue, and bone. Fisher et al. [13], who carried out a phase II NCI-sponsored extramural study of the same regimen, reported a 16% objective response in 35 patients with metastatic or unresectable renal-cell carcinoma; 2 subjects experienced complete regression of all tumor and 3 others showed partial responses involving a reduction of >50% of their total tumor burden. In other studies, the objective response rates obtained using IL-2-based immunotherapy were significantly lower than those reported by the NCI [14].

Nonetheless, there can be no doubt that in some patients with renal-cell carcinoma, IL-2 treatment can produce remarkable changes in the natural history of the disease. However, this group represents the minority of patients treated. Only 5% of subjects treated with IL-2 respond completely, and an additional 10%—15% respond partially. Thus far, these numbers have been so small that it has been difficult to demonstrate an overall survival benefit for IL-2-treated patients as a group.

The side-effects of IL-2 have been well documented and include fever, chills, malaise, nausea, vomiting, diarrhea, and other constitutional symptoms. The most common severe side effects, however, primarily involve renal and cardiopulmonary toxicity. IL-2 therapy induces prerenal azotemia along with hypotension, fluid retention, respiratory distress syndrome, oliguria, and low fractional sodium excretion. Importantly, cessation of IL-2 administration results in a rapid recovery and reversal of almost all side effects. Renal-function values return to baseline levels within 7 days in 62% of patients and within 30 days in 95% of cases [15, 16]. Treatment-related mortality is low, involving <2% of the patient population.

A newer approach to the immunotherapy of renal-cell carcinoma has been the use of TILs in combination with either IL-2 or IL-2 and IFN-alpha. TILs are predominantly T-cells that can be isolated from solid tumors when single-cell suspensions are cultured in the presence of IL-2 [17-19]. Unlike LAK cells, TILs can be expanded in large numbers and maintained in long-term cultures. Moreover, TILs have been demonstrated to be up to 100 times more effective than LAK cells in their therapeutic potency on a cell-to-cell basis [20]. TILs mediate cytotoxic activity against autologous and allogeneic tumor targets in vitro. Adoptively transferred TILs have exhibited long-term survival in mice [21] and have been found to localize preferentially in metastases in melanoma patients [22, 23]. In clinical trials involving 20 patients with metastatic melanoma, Rosenberg et al. [24] observed 1 complete response that lasted for >13 months and 10 partial responses of 2—9 months’ duration. These promising results formed the basis for efforts to develop TIL therapy for metastatic renal-cell carcinoma.

The initiation of TIL culture requires the procurement of fresh tumor tissue. TILs can be grown from both primary and metastatic lesions. We have previously described a method for the generation and expansion of TILs from fresh human renal-cell carcinoma [25]. These lymphoid cells exhibited significant antitumor activity when tested in short-term 51Cr release assays. The total cell recovery was 1.5 ± 2.2 × 10⁶ cells/tumor (range, 1 × 10⁶ - 5 × 10⁶ cells/tumor). The percentage of tumor cells in the suspension ranged from 6% to 75% (mean, 39.1%±3.3%). The remaining cells were predominantly lymphocytes. TILs within these tumors could be expanded in medium containing IL-2 for an average of 33.7 ± 4.5 days, resulting in a >65,000-fold increase in the total number of lymphocytes on average.

Phenotype analysis of TILs obtained from fresh renal-cell carcinoma cultures between days 16 and 23 revealed that the majority of TILs were cytotoxic/suppressor (CD8⁺ CD3⁺) cells. Continued in vitro expansion (for up to 50 days) produced a concomitant increase in the helper T-cell (CD4⁺) and pan-T-cell populations (CD3⁺) and a decrease in CD8⁺ and HLA-DR⁺ cells. As compared with LAK cells, these cells demonstrated higher levels of IL-2⁺ receptors (CD25⁺) and HLA-DR antigens. More recently, we have shown that profiles of lymphokine secretion by TILs may provide a useful marker for the functional characterization of TIL subsets and may provide correlates for the in vivo antitumor effects of these cells when they are adoptively transferred into cancer-bearing patients [26].

Phase I trials of TIL therapy of renal-cell carcinoma have been initiated at several institutions, including our own. Most of the toxicity encountered was related to IL-2 infusion. Fever and chills were the only side effects that were associated with TIL administration, and these were easily controlled with meperidine. No treatment-related deaths has been reported. Current efforts at UCLA are now under way to improve the potency of TIL immunotherapy by in vivo lymphokine priming prior to...