



The role of rational immunotherapy for renal cell carcinoma

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Metastases to distant organs are the principal cause of death from renal cell carcinoma (RCC). No commonly accepted therapy is available for disseminated RCC at present. The rationale for immunotherapy of RCC is based on the fact that there is no other therapy for advanced cases. Biologic therapies are the only current treatment modalities that have produced promising therapeutic results in metastatic RCC (mRCC). Therapy with cytokines usually has typical and sometimes severe side effects. Response rates and toxicity were higher with combined therapy. The administration of cytokines that augment the function of the immune system can be accomplished safely and without toxicity, provided a rational approach is used. The toxic effects that are frequently observed with combined therapy emphasize the need for careful selection of patients.

KEY WORDS: Carcinoma, Renal Cell; Immunotherapy; Cytokines

INTRODUCTION

Renal cell carcinoma is the most common malignant lesion of the kidney, accounting for approximately 85% of all renal cancers. Various studies have suggested a possible role for chromosome 3 in the etiology of nonfamilial renal cell cancer (RCC). Molecular genetic analysis of sporadic RCC and cell lines derived from human RCC reveals a loss of heterozygosity of chromosome 3p in approximately 90% tumors and nearly all cases of clear cell RCC. A variety of molecular changes in RCC proteins have been described, including p53, metalloproteinase, and telomerase (1-3). Metastases to distant organs are the principal cause of death from RCC. About 25% to 52% of diseased have occult metastases at the time of diagnosis. Of the patients with disseminated disease, 80% will die within 3 years after surgery (1,4). Metastatic RCC (mRCC) is refractory to chemotherapy, and median survival is usually less than a year. Patients with mRCC are difficult to treat from the aspect of urology, medical oncology and radiation oncology. There is no standard treatment for RCC. Results with hormone therapy and chemotherapy have been generally disappointing. The treatment of choice for localized renal cancer is surgical removal. The primary treatment for RCC is radical nephrectomy with lymph node dissection. Even patients with localized disease

who undergo surgical nephrectomy have a significant relapse of approximately 30%. Thus there is a clear need for systemic therapy to reduce the risk of relapse and improve survival and quality of life in patients with advanced disease (1,4,6).

Adjuvant therapy may include surgical excision of distant metastases, radiation therapy, chemotherapy, and immunotherapy and it can be divided into prophylactic treatment for metastatic disease. The role of adjuvant radiation therapy remains controversial. Randomized studies similarly have shown no improvement in the survival rate of patients who received postoperative radiation therapy. Radiation may be helpful for palliation. Brain metastases may be reduced in size by radiation. Bone pain from metastases is particularly well palliated in this way (5,7).

Hormone manipulations have been used for renal cancer for several decades. In prospective randomized trial with progesterone therapy, there was no benefit from adjuvant hormone therapy. Hormone therapy (testosterone, progesterone, estrogen antagonists) in mRCC has not improved the survival of patients (5).

Chemotherapy is not a therapy of choice for advanced RCC. One possible explanation is multidrug resistance (MDR) mediated by p-glycoprotein and other mechanisms. Normal proximal tubules and RCC both express high levels of p-glycoprotein. Calcium channel blockers that interfere with the function of p-glycoprotein may diminish the resistance to vinblastine and anthracyclines blockers or other drugs (6,7).

Spontaneous regression of malignant tumors and/or metastases is a rare event. RCC is an immunogenic tumor. The frequency of spontaneous regression in human RCC is estimated between 0.5% and 7% of all cases.

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BIOLOGICAL THERAPIES

Biologic therapies are the only current treatment modalities that have produced promising therapeutic results in mRCC (4,8,9,10). The rationale for immunotherapy of RCC is based on the fact that there is no other therapy for advanced cases. The cytokines are the only drugs that have been shown to induce tumor regression in some patients. This provided the rationale for investigating interferon alpha in patients with mRCC and has led to the current situation where interferon alpha is regarded as an important therapeutic option in the management of patients with advanced disease.

Recombinant interleukin-2 and interferon alpha are the most widely used cytokines in the treatment of mRCC. The biological agents interferon alpha and interleukin-2 have been found to induce objective response rates from 15% to 20% as monotherapy and are now being investigated as components of combined regimens. Modifications of this combination have included the use of low-dose intravenous or subcutaneous immunotherapy in combination with chemotherapy, without a demonstrable advantage and the use of cytokine therapy with interferon-activated tumor-infiltrating lymphocytes (11-15).

The results of the randomized studies, which have been completed to date involving interferon alpha based regimens, clearly indicate that interferon alpha is active in this disease. Patients who are most likely to respond and who should be offered interferon alpha therapy are those who are less than 70 years old, with good performance status, and metastases in either the lungs or the lymph nodes (17,18). Various studies have attempted to identify other possible prognostic factors, which could be used to identify patients most likely to benefit from interferon alpha based therapy (4,6,17,18).

Future advances in interferon therapy are likely to be based on emerging information about the cellular actions of interferon and interferon-related signal transduction pathway. As the components of these pathways become more clearly understood, potential target for interferon-mediated effects are likely to be identified (16,18, 27).

At least 14 studies that have been published to date report the results of interferon alpha and interleukin-2 combined regimens (4). The average response rate for these studies, which involved over 300 patients, was 22% and ranged from 0% to 50%. The recently published CRECY study is important multicenter randomized study. It compares interferon alpha-2a monotherapy with IL-2 monotherapy and with a combination of the two agents. The results of this study, which were first presented at ASCO 1996, demonstrated a significant event-free survival benefit at 1 year for combination therapy (10,19-21). The overall response rate was also significantly higher in patients receiving the combined regimen. The high-dose IL-2 regimen employed in this study was associated with unacceptable toxicity. Response rates and toxic-

ity were higher with the combination therapy (22,23).

Cytokines are molecules that have pleiotropic activity and crucial role in the regulation of the immune response. Therapy with cytokines usually has typical and sometimes severe side effects (22). The higher response rate and longer event-free survival obtained with a combination of cytokines must be balanced against the toxicity of such treatment. The administration of cytokines that augment the function of the immune system can be accomplished safely and without toxicity, provided a rational approach is used.

Rational recombinant interleukin-2 (rIL-2) immunotherapy is based on the knowledge of how the immune system is regulated, sound pharmacological principles and the structure-activity relationship of the interleukin-2/interleukin-2 receptors interaction. The recognition of the above stated facts and principles should establish efficacy without toxicity (23). Reducing the toxicity of regimens containing interleukin-2 is therefore a high priority for future studies. The key is to administer ultra-low doses of rIL-2 that do not produce toxicity. The toxic effects frequently observed with combined therapy emphasize the need for careful selection of patients. When combining rIL2 with other biologic agents or chemotherapy, it is important to keep in mind that objective remissions, though important, are not the gold standard clinical endpoint. The gold standard endpoint for rIL-2-based therapy should be the induction of long-term survival (25,26).

The advances being made with biological treatment are still modest. The further research is required to improve the outlook of patients with advanced RCC. Development of immunotherapies such as immunomodulatory cytokines, vaccination and gene therapy with cytokine genes offer promising approaches to improve on current management options (26).

OUR EXPERIENCE

In our study 55 patients were treated; forty patients were given interferon only 2 to 3 times a week in dose of 6 MIU up to the total dose of 180 MIU; fifteen patients were treated with the combination of interferon and interleukin-2 subcutaneously during seven weeks. Clinical, biological, immunological and toxic effects were followed up before and after the therapy. The number of peripheral CD3, 4, and 8 lymphocytes was determined by monoclonal antibodies on Profile-II, NK toxicity according to Bruner's method, and ELISA assay was used for determination of antibodies to interferon. Toxic effects were evaluated according to WHO criteria (6,10,28,29).

Subcutaneous interleukin-2 based therapy is accompanied with mild side effects and within tolerable toxicity, and thus can be applied on an outpatient basis. Interferon therapy causes constitutional, hepatic and hematological toxic effects of lower degree. Combined therapy results in lymphopenia (from day 1 to 5),

recurrent lymphocytosis (days 6 and 7), the higher number of NK cells, but without significant changes of peripheral CD3, 4, and 8 lymphocytes. These changes are the result of complex immunomodulated effects of interleukin-2 and interferon. None of the prognostic factors for the most common toxicity have been determined so far (10, 29-32).

The future of immunotherapy seems to be bright and the first, although modest, positive results are visible, especially in case of patients with metastatic renal carcinoma.

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