

# Principles and Practice of Genitourinary Oncology

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## CHAPTER 84

# Systemic Immunotherapy for Genitourinary Neoplasms

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Despite advances in prevention and early detection, refinement in surgical technique, and improvements in adjuvant radio- and chemotherapy, the ability to cure cancer remains elusive in many patients. The continuing challenge of cancer treatment is the successful management and eradication of metastatic disease. Over the past decade, it has become increasingly apparent that effector cells of the immune system play an important role in the recognition and elimination of neoplastic cells. Recently, therefore, cancer therapies have been directed at modulating and exploiting the components of the immune system. Specific molecules (i.e., cytokines) have been targeted because of their involvement in the initiation and maintenance of immune surveillance and response. Early clinical studies with systemic cytokine infusions demonstrated tumor regression, but usually at the cost of substantial toxicity and side effects. Refinements have included the concept of adoptive immunotherapy using lymphokine-activated killer (LAK) and tumor-infiltrating lymphocyte (TIL) cells, with the intent to increase the amount of tumor regression while reducing toxicity. Current research focuses on utilizing gene therapy as a mechanism by which the immune response to neoplastic tissue can be modulated and improved.

Renal cell carcinoma and bladder cancer are prime examples of diseases where immunotherapy holds promise for achieving improved cure rates. Metastatic renal cell carcinoma has a poor prognosis, with an average survival of only 6 to 12 months from the time of diagnosis. Recent developments in immunotherapy, however, have resulted in an improved outlook. The incidence of bladder cancer is on the rise, yet the mortality peaked in the mid 1980s and continues to decline. Nonetheless, the number of patients with recurrent or progressing superficial bladder tumors after treatment with transurethral resection and established intravesical chemotherapy protocols remains at 50% of those treated. It is in this patient population where innovation in traditional treatment methods is most needed and immunotherapy can fill the void. Investigations into applying immuno- and gene therapy for the treatment of metastatic prostate cancer have been initiated, and early results appear promising (although it is too soon for definitive conclusions).

This chapter explores the role of immunotherapy in the treatment of advanced genitourinary neoplasms. Principles of immunotherapy will be discussed, along with reviews of the most current immunotherapeutic applications to the treatment of renal cell, bladder, and prostate cancers. Future treatment modalities will also be outlined.

### OVERVIEW: HUMORAL AND CELLULAR IMMUNOLOGIC EFFECTOR CELLS\*

Although immune responses have traditionally been divided into two categories—humoral, mediated by antibody-secreting B-lymphocytes, and cellular, mediated by T-lymphocytes—they involve interactions from both cell types, with additional support from a third, the antigen-presenting cell (APC). After initial MHC-restricted activation by APCs, T-lymphocytes act through either direct contact with target cells, or via secreted cytokines, agents that augment target cell behavior through a variety of mechanisms.

Initially, T-lymphocytes were divided into T8 (CD8+) and T4 (CD4+) elements, based on specific surface molecules that appeared to influence their behavior. CD8+ cells were determined to be cytotoxic, and were therefore named cytolytic T lymphocytes. They secrete a limited spectrum of cytokines, such as interleukin 3 (IL3), interferon  $\gamma$  (IFN $\gamma$ ), and granulocyte-monocyte colony-stimulating factor (GM-CSF). CD4+ elements can now be further divided functionally, by the cytokines they secrete, into Th<sub>1</sub> cells, which produce IL2, IL3, IFN $\gamma$ , lymphotoxin, and GM-CSF, and Th<sub>2</sub>, which produce GM-CSF, IL3, IL4, IL5, IL6, and IL10. These cytokines have widespread effects on APCs, B lymphocytes, and other T lymphocytes, and are discussed later in this chapter.

Once activated by antigen, cytokines, or APCs, B lympho-

\* For a thorough review of the principles of immunology, please refer to William Paul's text *Fundamental Immunology*. (New York: Raven Press, 1993).



cytes proliferate into plasma cells, which subsequently produce antibodies. "Monoclonal antibodies" are laboratory-designed antibodies produced with specific characteristics and in high quantity. They have come to play a significant role in medical research. Currently, however, monoclonal antibodies have had little utility in the treatment of genitourinary neoplasms. When renal, prostate, or bladder tumor-specific peptides can be identified, isolated, and characterized, monoclonal antibodies to that antigen can be produced, attached to cytotoxic agents, and perhaps used to directly target and destroy those tumor cells. At this time, however, this is mostly conjecture. T lymphocytes, on the other hand, maintain a primary role in current immunotherapeutic protocols for advanced genitourinary cancers, and will be discussed further throughout this chapter.

## FUNDAMENTALS OF IMMUNOTHERAPY

The immune system contributes to the surveillance and destruction of tumor cells.<sup>1</sup> Multiple cellular and humoral immune effectors inhibit tumor proliferation. Cellular mediators with antitumor activity killer (MHC-restricted cytotoxic T cells (Tc), natural killer (NK) cells, and lymphokine-activated killer (LAK) cells. The goal of immunotherapy in the treatment of advanced cancers is to sensitize these immune effector cells to tumor antigen and produce a cytolytic response directed at the sites of tumor with minimal systemic toxicity. The application of immunotherapy is limited to *immunogenic* malignancies, those tumors which are known to be vulnerable to immune-mediated cytotoxicity. Renal cell carcinoma and bladder cancer are both immunogenic, and therefore should be responsive to immunotherapy. Preliminary in vitro data suggest that prostate cancer cells can also respond to immunomodulation by cytokines.<sup>2,3,4</sup> Modern immunotherapy can be applied to neoplastic disease in one of several manners: (1) by systemic or locoregional infusion of immunostimulatory agents; (2) by passively transferring immune cells with antitumor reactivity (such as LAK or TIL cells) to the tumor-bearing host to attack sites of cancerous cells (*adoptive immunotherapy*); or (3) by vaccination with tumor cells transformed with genes or other immune stimulators to promote the generation of immune lymphoid cells with anti-tumor activity, or systemic or locoregional transfection of tumor cells with genetic material that can either induce tumor cell differentiation, cause direct cytolytic activity, produce regional cytokine secretion, or enhance MHC receptor expression ("gene therapy"). This latter method is referred to as *active immunotherapy* and intensive investigation is currently underway.

### Adoptive Immunotherapy

Adoptive immunotherapy involves the in vitro growth, expansion, and immune-modification of lymphoid cells (NK and T cells) prior to reinfusion back into the host.<sup>5,6,7</sup> One such example is TIL therapy, which has been shown to cause regression of bulky tumors in a variety of animal tumor models and in humans. TILs are lymphoid cells isolated from fresh solid tumors upon co-culturing a tumor-cell suspension with the cytokine interleukin-2. After expansion of these cells in culture, which usually takes 3 to 4 weeks, TILs are reinfused into the

patient in the hope that these cytotoxic T lymphocytes will recognize, home to, and destroy tumor deposits throughout the body.<sup>6,8</sup> Our own data at UCLA using TILs in patients with advanced renal cell carcinoma resulted in a response rate of 34% (see below).

### Active Immunotherapy

Active or specific immunotherapy refers to the immunization of a patient with agents that will increase the host immunologic response against the tumor. The first report dates to 1971 when a patient with metastatic renal cell carcinoma was cured after receiving serum obtained from a relative, also with renal cell carcinoma, but in remission.<sup>9</sup> Current research is concentrated on creating tumor vaccines. During the intervening 20 years, the study of immunotherapy has introduced systemic cytokine treatment modalities as well as the adoptive immunotherapeutic techniques of LAK cells and TILs into the war against cancer.

Tumor vaccine protocols utilize the ability of cytokines to increase tumor cell immunogenicity, thereby increasing the ability of the host immune system to recognize and destroy cancer foci. Autologous tumor cells are transfected in vitro with cytokine producing genes. These transfected cells, now producing cytokines and expressing increased MHC class I antigens, are retransplanted into the host where they stimulate a tumor-specific immune response. Cytokine production occurs only at the implant site, thereby producing a strong antitumor response without systemic toxicity. The stimulated immune effector agents can then diffuse throughout the host to hunt down and destroy other tumor foci and provide immunological memory to the host. Studies in animals with subcutaneously placed vaccines have demonstrated potent, specific, and long-lasting antitumor immunity with protection upon rechallenge with tumor.<sup>10,11</sup>

Another approach to modulating the host immune response is by increasing the tumor's immunogenicity in vivo by systemic or intralesional injections of genetic elements that will transfect tumor cells and either enhance MHC class I expression, stimulate regional cytokine production, or introduce foreign antigenic material.<sup>12</sup> Such genetic material includes cytokine, suicide, and suppressor genes. This modality of gene therapy is currently under investigation, and is so far limited by technical difficulties involving efficient and safe gene delivery systems.

### Cytokines

Cytokines are important elements in the antitumor response: they are soluble factors that are responsible for communication between cells of the immune system. In addition to direct tumoricidal effects, they also activate effector components of the immune system.<sup>1,13-19</sup> The introduction of cytokine genes into tumor cells has been repeatedly proven to enhance antitumor immune responses in both in vitro and in vivo studies. The following are the cytokines which have shown the most promise in genitourinary neoplasms. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) has direct effects on neoplastic cells resulting in cell death. Interferon- $\alpha$  (IFN- $\alpha$ ) induces a marked increase in the surface expression of class I MHC antigens in addition to direct antitu-

mor activity. It also up-regulates adhesion molecule expression on the surface of tumor cells, aiding the immune response. Interferon- $\gamma$  (IFN- $\gamma$ ) induces a marked increase in the surface expression of class I and II MHC antigens. Interleukin-2 (IL-2) is produced by activated T cells and causes proliferation of cytotoxic T (Tc), natural killer (NK), and LAK cells capable of lysing autologous, syngeneic, or allogeneic tumor cells, but not normal cells. IL-2 has no direct antitumor effect, but secretion of IL-2 from tumor cells abrogates tumorigenicity by stimulating the activation and proliferation of immune effector cells.<sup>20</sup>

## IMMUNOTHERAPY FOR METASTATIC RENAL CELL CARCINOMA

In 1996, 30,600 Americans will be diagnosed with renal cell carcinoma, accounting for 2 percent of all adult malignancies.<sup>21</sup> Surgically unresectable disease has a poor outcome, as no successful radio- or chemotherapy strategies have been devised.<sup>22</sup> The natural history of renal cell carcinoma is not always predictable, and spontaneous regression of metastases after nephrectomy does occur, albeit rarely (less than 1%). Early observations of spontaneous regression, along with the discovery of circulating humoral and cellular elements in such patients, delayed growth of metastatic lesions, and varying tumor doubling times, suggested involvement of the immune system in the natural host response to this neoplasm.<sup>23</sup> Since then, renal cell carcinoma has become a paradigm for the immunotherapeutic approach to treating solid organ malignancies.

Initial approaches to immunotherapy utilized nonspecific immune stimulators, such as bacillus Calmette-Guérin, or xenogeneic RNA-treated lymphocytes (probably a stimulator of interferon production). Despite initial enthusiasm,<sup>24-26</sup> this approach ultimately yielded no significant improvement in prognosis.<sup>27</sup> Several studies with BCG showed some initial benefit although larger randomized studies were not performed.<sup>28-30</sup> A similar situation holds for *Corynebacterium parvum*<sup>31</sup> and transfer factor,<sup>32</sup> two other nonspecific agents no longer in vogue. One third of the patients enrolled in a pilot study to assess the antitumor activity of 1,2-benzopyrene responded to treatment, yet subsequent phase II studies with this nonspecific agent were associated with only a 6% response rate. These nonspecific agents are now mainly of historical interest with regards to treating renal cell carcinoma.

### Biologic Therapy with Cytokines

The isolation, identification, and molecular cloning of IL-2 revolutionized the field of cancer immunotherapy and significantly altered the treatment of metastatic renal cell carcinoma.<sup>33,34</sup> Since then, other immunostimulatory cytokines have been identified and purified. With the advent of recombinant DNA technology, the ability to produce large quantities of these cytokines has resulted in their wide-spread use and, in a relatively short period of time, these agents have become an accepted treatment for metastatic disease. To date, most studies investigating the use of cytokines in the treatment of metastatic renal cell carcinoma have used IFN- $\alpha$ , IL-2, combinations of these cytokines, or adoptive immunotherapy with TILs or LAK cells. The role

of a new generation of cytokines such as IL-4, IL-7, IL-12, and GM-CSF is currently under investigation.

### Interferon Alpha and Gamma

Research at UCLA in the early 1980s was the among the first to demonstrate the effectiveness of IFN- $\alpha$  in the treatment of metastatic renal cell carcinoma.<sup>35</sup> Independent studies at the same time confirmed the regression of metastatic disease with objective response rates of 16% to 26% lasting an average of 8 to 10 months.<sup>36,37</sup> These numbers have not changed significantly in the past decade, despite numerous phase II trials and attempts at modifying doses and dosing schedules.<sup>38-49</sup> Table 84-1 summarizes the major studies of the past decade, demonstrating a reproducible response rate of 15-20 percent and a response duration of 8 to 10 months. Responses appear independent of the preparation and dosing used. Improved response rates of 30% and durable clinical responses lasting more than 27 months can be seen in a select subset of patients treated with IFN- $\alpha$ .<sup>45,47</sup> These patients have had a prior nephrectomy, no previous chemotherapy or radiation therapy, good to excellent performance status, and primarily pulmonary metastases. (Lung metastases appear more responsive to IFN- $\alpha$  therapy than those of other viscera.<sup>43</sup> At UCLA, survival rates increased from 49 to 115 weeks in IFN- $\alpha$  treated patients with these favorable prognostic variables.<sup>47</sup>

Side effects of IFN- $\alpha$  treatment include fever, chills, myalgia, anorexia, and headache. These are usually associated with the initial dosing and often improve spontaneously with continued administration of the drug. Reversible hematologic and hepatic changes are occasionally noted, but they, too, usually resolve without necessitating changes in dosing.<sup>50,51</sup>

Combining accessory agents with IFN- $\alpha$  has been investigated as a means of increasing responsiveness and decreasing

TABLE 84-1. Phase II trials of interferon-alpha for the treatment of metastatic renal cell cancer

Investigators	Patients	Response
DeKernion et al, 1983 <sup>35</sup>	43	16.5%
Quesada et al, 1983 <sup>36</sup>	19	26%
Neidart et al, 1984 <sup>41</sup>	33	15%
Figlin et al, 1985 <sup>48</sup>	23	13%*
Quesada et al, 1985 <sup>37</sup>	50	26%
Kirkwood et al, 1985 <sup>38</sup>	30	23%
Umeda and Nijjima, 1986 <sup>40</sup>	226	17.7%
Fossa et al, 1986 <sup>57</sup>	18	33%*
Muss et al, 1987 <sup>45</sup>	97	7%†
Creagan et al, 1987 <sup>49</sup>	29	34%‡
Sarna et al, 1987 <sup>47</sup>	43	14%§
	22	14%*
Figlin et al, 1989 <sup>39</sup>	18	26%
Minasian et al, 1993 <sup>44</sup>	159	10%*
Total	651	20%

\* Addition of vinblastine (0.15 mg/kg).

† Select subpopulation (+ prior nephrectomy, - prior chemotherapy, - bone mets) had 23% response rate.

‡ Aspirin, 600 mg PO qid.

§ Select subpopulation (+ prior nephrectomy, - prior chemotherapy, - bone mets) had 24% response rate.

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