Renal Cell Carcinoma: Recent Progress and Future Directions

Peter Mulders, Robert Figlin, Jean B. deKernion, Robert Wiltout, Marston Linehan, David Parkinson, William deWolf, and Arie Beldigrun

Departments of Urology [P. M., J. B. d. K., A. B.] and Medicine/Division of Medical Oncology [R. F.], University of California at Los Angeles School of Medicine, Los Angeles, CA 90024; National Cancer Institute [R. W., M. L.], Bethesda, MD 20892; Novartis, Inc. [D. P.], Harvard Beth Israel Hospital [W. d. W.]

Introduction

Approximately one-third of patients with RCC have metastatic disease at initial presentation or on relapse, and the prognosis for metastatic RCC remains highly unfavorable, because RCC is usually resistant to radiotherapy and chemotherapy. Therefore, new treatment modalities including novel immunotherapeutic approaches are being investigated and are promising.

rIL-2 is currently the only immunotherapeutic agent approved for use in RCC by the United States Food and Drug Administration and is the current gold standard for treating metastatic RCC. Treatment with high-dose i.v. bolus rIL-2 regimens produces objective response rates of approximately 20%, and the majority of complete responses are durable for 3 or more years. Immunotherapy with rIL-2 has produced significant improvements in long-term survival and has led to the investigation of a variety of other immunotherapeutic approaches for treating metastatic RCC.

At a recent symposium held in September 1996 in Washington, D.C. and sponsored by the National Cancer Institute, clinicians and researchers convened to discuss recent progress and future directions in the diagnosis and treatment of RCC. Presentations focused on two areas of active research: (a) understanding the molecular genetics and biology of RCC; and (b) new immunotherapeutic strategies. Recent developments in these areas are generating a great deal of enthusiasm. Several genes have recently been identified that may contribute to the development of several hereditary forms of RCC. Identification of these genes may lead to improved screening tests and new therapeutic options. Advances in immunotherapy for RCC are also exciting. New combination regimens, adoptive immunotherapy, gene therapy, and therapeutic mAbs are currently being investigated, and many of these approaches are showing promise. Other areas of research, including multidrug resistance and host factors that influence the antitumor immune response, were also discussed.

Epidemiology.

In recent years, the incidence of RCC has increased dramatically (54% from 1975 to 1990), and in 1996, approximately 30,000 new cases were diagnosed in the United States (1). In the same year, an estimated 12,000 RCC-related deaths occurred in the United States (2). The increased incidence of RCC in recent years may be linked to certain risk factors such as smoking, obesity, high-protein diets, and hypertension (3). For example, smoking is associated with a 40% increased risk. Hypertension, with the associated use of diuretics and antihypertensive drugs, is also associated with a slightly increased risk of RCC (4, 5).

Nearly half of all RCC patients present with localized disease, one-quarter present with stage III disease, and nearly one-third of patients present with metastatic disease (1). In addition, as many as 40% of all patients treated for focal tumors will ultimately relapse with metastatic disease (6). The prognosis for untreated patients with metastatic disease is unfavorable, with a 3-year survival rate of less than 5% (7). Among patients who develop metastases within 1 year of nephrectomy, the 2-year survival rate is likewise very poor. In a few rare cases, however, in which patients develop metastases more than 2 years postnephrectomy, long-term survival in excess of 5 years has been observed (8).

Pathology.

The majority of RCC tumors have a distinct clear cell histology; however, approximately 25% of cases exhibit a mixed histology (9). The Mainz classification system defines clear, chromophilic, and chromophobic histological types as distinct morphologies with clearly distinguishable cellular, enzymatic, and genetic characteristics (10). The importance of diagnosing and appropriately treating multifocal disease has also been addressed. Multifocal disease is associated with an increased incidence of papillary and mixed histologies.

Molecular Genetics.

Several tumor suppressor genes, including the VHL gene, the WT1 gene, and the tuberous sclerosis gene 2, have been implicated in the development of sporadic as well as hereditary tumors in the kidney. The WT1 tumor suppressor gene may regulate the activity of two key oncogenes, hcl-2 and c-geye, that may contribute to the development of RCC (11). Key genetic components in the pathogenesis of RCC will likely be identified through studies involving the Eker rat model of hereditary predisposition to RCC. Several participants also presented evidence of increased telomerase activity in RCC relative to normal renal tissue, suggesting that this enzyme may play a role in the pathogenesis of RCC and could serve as a useful diagnostic marker.

To identify genes involved in the origin of clear cell RCC, studies were performed of a hereditary form of clear cell RCC associated with VHL. VHL disease is a hereditary cancer syndrome in which affected individuals are at risk for the development of tumors in the adrenal, pancreas, cerebellum, spine, inner ear, retina, and epididymis. VHL patients can develop bilateral multifocal renal tumors and cysts, which can appear at an early age (12). The renal tumors that develop in VHL patients are uniformly of clear cell type (13). Genetic linkage analysis identified the VHL gene, which is located on the short arm of chromosome 3 (14). The VHL gene has been found to have the characteristics of a classic tumor suppressor gene. In tumors from patients with VHL, both copies of the VHL gene are inactivated, one copy by germ-line mutation and the other by loss of heterozygosity. The VHL wild-type allele is lost early in the development of VHL renal lesions (15). To determine if the VHL gene is associated with sporadic renal tumors, VHL gene mutation and loss of heterozygosity analysis was performed on cell lines and tumors from patients with nonhereditary, clear cell RCC. VHL gene mutations and loss of...
heterozygosity were found in a high percentage of clear cell RCCs (16, 17). Additionally, Herman et al. (18) have shown that hypermethylation of the normally unmethylated CpG island of the 5' region of the VHL gene provides another mechanism for inactivation or silencing of the VHL tumor suppressor gene in clear cell RCC.

In a study of the function of the VHL protein, Lee et al. (19) have shown that there is a tightly regulated cell density-dependent transport of VHL into and out of the nucleus. The VHL protein is found to be predominantly in the nucleus of cells grown under sparse conditions. When the cells are densely grown, the VHL protein is mostly in the cytoplasm (19). Studies of VHL-associated proteins have provided critical insights into the potential function of the VHL kidney cancer tumor suppressor gene. Duan et al. (20) and Kibel et al. (21) have shown that the cellular transcription factor, Elongin (III), is a target of the VHL protein. The VHL protein binds specifically and tightly to the Elongin B and C regulatory subunits of the Elongin A,B,C heterotrimer that activates transcription elongation by RNA polymerase II (20, 21). Pause et al. (22) have recently shown the trimeric pVHL-elongin B-C complex associates with Hs-CUL-2, a member of the cullin multigene family (22). The finding that the yeast homologue of Hs-CUL-2, Cdc53, targets cell cycle proteins for degradation has suggested additional studies to determine the potential role of VHL in cell cycle regulation. Additional functional studies of the VHL gene have investigated its role in regulation of VEGF. Both sporadic clear cell RCC and the tumors associated with VHL are markedly vascular. Many of these tumors express high levels of VEGF. The VHL protein has been found to be a negative regulator of the hypoxia-inducible genes, including VEGF. The VHL protein can regulate VEGF expression at a posttranscriptional level. It has been shown that inactivation of VHL can be associated with a loss of VEGF suppression, which may play a role in the formation of tumor-associated angiogenesis (23, 24).

A new form of hereditary RCC, HPRC, has recently been described (25, 26). Affected individuals are at risk to develop multifocal bilateral papillary RCC. HPRC is distinct from VHL; patients do not develop the clinical manifestations of VHL, and germ-line VHL gene mutations are not found. Schmidt et al. (27) localized the HPRC gene to a region on the long arm of chromosome 7. Using a positional mapping approach, the MET proto-oncogene was identified as a strong candidate for the HPRC gene. In the germ-line of affected HPRC individuals, missense mutations located in the tyrosine kinase domain of the MET gene were identified (27). Additional studies are underway to more accurately determine the phenotype of HPRC and to determine if other malignancies are associated with this hereditary cancer syndrome.

Therapeutic Challenges

A major challenge to the development of effective therapies for the treatment of metastatic RCC is its resistance to both chemotherapy and radiotherapy. RCCs typically exhibit a multidrug-resistant phenotype associated with expression of the multidrug resistance gene (MDR-1; Ref. 28), and objective responses to chemotherapy occur in <10% of treated patients (29). However, RCC is known to be immunogenic, and immunotherapy with biological response modifiers has had some measure of success. Indeed, significant clinical responses have been achieved with rIL-2, which is currently the standard therapy for metastatic RCC patients with good performance status (30). Although rIL-2 has no direct cytotoxic antitumor effect, its widely documented inhibitory effect on the growth of human cancers, including colon carcinoma, bladder carcinoma, and melanoma, stems from its ability to activate an antitumor immune response (31).

With the success of rIL-2 therapy, and based on the pioneering work of Dr. Steven Rosenberg, in metastatic melanoma and RCC at the National Cancer Institute, a variety of approaches to immunotherapy are being investigated for the treatment of metastatic RCC. These include (a) immunomodulation with biological response modifiers; (b) adoptive immunotherapy, which involves the transfer of cells with antitumor activity; (c) therapeutic tumor-specific mAbs; (d) vaccines designed to stimulate a specific antitumor immune response; and (e) gene therapy. Current and future preclinical and clinical research on immunotherapy for metastatic RCC are summarized in Tables 1 and 2.

Biological Response Modifiers

rIL-2. rIL-2 obtained United States Food and Drug Administration approval in 1992 on the basis of demonstrated safety and efficacy in clinical studies involving 255 patients with RCC who were treated with high-dose rIL-2 regimes (35). The cumulative experience with high-dose rIL-2 therapy has demonstrated approximately a 15% objective response rate (complete and partial responses), mostly in patients with good clinical performance status, with a median survival of approximately 40 months for patients achieving a complete response and 24 months for patients achieving a partial response. The objective response rate for RCC patients treated at the National Cancer Institute with high-dose i.v. bolus rIL-2 before December 1992 was 20% (36). More than 75% of patients achieving a complete response remained disease free for 3+ years, and some complete responses have been durable for 5+ years. The major challenge has been to develop new regimens and new strategies to further improve survival with manageable toxicity.

Dr. James C. Yang, presented results involving 260 patients in an ongoing three-armed randomized trial designed to establish the optimum dose of rIL-2. This trial compared 720,000 IU/kg i.v. bolus every 8 h (high-dose i.v. bolus group), 72,000 IU/kg i.v. bolus every 8 h (low-dose i.v. bolus group), and 120,000 IU/day s.c. for 5 days each week (s.c. group; 40). The objective response rates were 21% in the high-dose i.v. bolus group compared with only 11% in the low-dose i.v. bolus group, and response durations were significantly longer in the high-dose group. Toxicity, including hypotension, dyspnea, thrombocytopenia, malaise, and disorientation, was significantly greater with the high-dose regimen, and approximately 50% of patients in this group required treatment for hypotenston compared with less than 5% in the low-dose group. The response rate and toxicities observed in the s.c. group were similar to those observed in the low-dose i.v. bolus group. Although the high-dose i.v. bolus regimen is associated with significant toxicity, it seems to be the most effective rIL-2 regimen in terms of response rate, duration of response, and overall survival. With adequate monitoring of patients, it can be tolerated without risk of treatment-related mortality.

Dr. Janice Dutcher addressed the role of nephrectomy in selected patients who responded to rIL-2 treatment. In a study reported by Bennett et al. (57), four of six patients whose renal tumors progressed after immunotherapy exhibited no evidence of residual disease after resection and have remained disease free for nearly 5 years.
The acceptance of rIL-2 as the standard therapy for metastatic RCC has led to the investigation of other biological response modifiers for treating this disease. These include rIFN-α, rIFN-γ, and rIL-2, alone or combined with other agents such as CRA or adoptive immunotherapy.

rIFN-α. Since the first clinical trials in 1983 suggesting that rIFN-α was effective in metastatic RCC, a large number of studies have been conducted. The objective response rate from the treatment of more than 900 patients in 13 clinical trials with rIFN-α was 18.4%, and response durations ranged from 6–10 months; however, complete responses are rare (30, 33, 49). Despite the large number of studies investigating the efficacy of rIFN-α in metastatic RCC, the optimal dose and schedule have not been determined because of significant variability in reported response rates, which may stem from differences in regimens and patient populations. The published data do suggest, however, that a dose of 10–20 MIU/day produces optimal response with this combination being equivalent to or greater than that reported with both regimens; however, no large randomized trial has demonstrated an objective response rate of 15% (43). A United States Cooperative Group randomized, open-label trial investigated the efficacy of 100 μg/week s.c. in 200 patients who had undergone prior nephrectomy or embolization (44). The overall response rate in this study was only 3%; however, this dose of rIL-2 was well tolerated. A similar study conducted in Canada failed to demonstrate any clinical benefit of rIFN-γ therapy. Results of this study will be published in the near future.

Combination Therapy With rIFN-α and rIL-2. Preclinical murine tumor models have demonstrated synergistic antitumor effects with the combination of rIFN-α and rIL-2, establishing a compelling rationale for their combined use (61). The mechanisms of synergy are unclear, but administration of rIFN-α may augment the immunogenicity of tumor cells by enhancing expression of MHC antigens and presentation of tumor-associated antigens to T lymphocytes.

Clinical trials have established the safety and efficacy of combination therapy with rIFN-α and rIL-2 in metastatic RCC. The available data from 1200 patients treated with this combination collectively demonstrate an objective response rate of approximately 20%, and approximately 5% of patients achieved a complete response. Responses overall have occurred at all disease sites, including bone, intact primary tumors, and visceral metastases, and have included patients with large tumor burdens or bulky individual lesions. Some durable complete responses have been observed. The frequency of response with this combination is equivalent to or greater than that reported with rIL-2 alone, and durable complete responses are reported with both regimens; however, no large randomized trial has directly compared the efficacy of rIL-2 alone versus rIL-2 plus rIFN-α.

Several studies have also investigated the combination of rIL-2, rIFN-α, and 5-fluorouracil for metastatic RCC, with encouraging results (46, 47). In a Phase 2 outpatient study investigating the efficacy of s.c. rIL-2 (20 MIU/m²) and rIFN-α (6–9 MIU/m²) plus i.v. bolus 5-fluorouracil (750 mg/m²), an overall response rate of 39% was observed (11% complete responses and 28% partial responses) (45). Stratiﬁcation of patients by risk factors disclosed a significant survival advantage with this combination compared with single-agent rIL-2 in...
low- and intermediate-risk patients. Others have reported similarly.

rIL-12. Preclinical and Phase I clinical trials are currently investigating the biological effects of rIL-12 and its antitumor activity in metastatic RCC. IL-12 is thought to induce expression of other cytokines and chemokines. Preclinical experiments conducted by Dr. Jon Wigginton et al. have shown that administration of weekly pulses of rIL-2 in combination with rIL-12 additively enhanced the priming of macrophages for nitric oxide production in culture and reversed tumor growth in mice far more effectively than did either agent alone (32).

Dr. Robert Wiltrout also speculated that the combination of rIL-2 plus rIL-12 may induce some antiangiogenic effects.

Dr. Ronald M. Bukowski presented interim data from two ongoing Phase I clinical trials investigating the safety and effectiveness of rIL-12 in metastatic RCC. The first trial is investigating a fixed dose of 0.1 to 1 μg/kg, and the second is a do-escalation trial starting at 0.1 μg/kg and escalating to the maximum tolerated dose, which has not yet been reached. Tumor regression has not yet been observed in these studies, but some changes in rates of tumor growth have been documented. In 50% of patients, an induction of IFN-γ RNA was observed. In addition, two IFN-inducible chemokines were detected in rIL-12-treated patients, suggesting that rIL-12 induces IFN-γ expression, resulting in an enhanced antitumor immune response.

Adoptive Immunotherapy

A variety of adoptive immunotherapeutic approaches have been investigated in RCC, including adoptive transfer of TILs, lymphokine-activated killer cells, and ALT. Lymphocytes with potential cytotoxic antitumor activity can be isolated from peripheral blood, tumor-draining lymph nodes, or tumor tissue. These cells are subsequently expanded ex vivo and reinfused into the patient, often in combination with biological response modifiers, with the hope of improving the rate and durability of response.

TILs. TILs can be isolated from the patient’s tumor, expanded ex vivo in rIL-2, and reinfused, typically in conjunction with rIL-2 and/or rIFN-α therapy or chemotherapy. In an early study, 12% of RCC patients treated with rIL-2 plus TILs achieved a clinical response (48). The University of California at Los Angeles experience with these regimens has been more favorable according to Dr. Arie Belldegrun. Of the 55 patients treated with a combination of rIFN-α and TILs, and low-dose i.v. rIL-2, 35% achieved a clinical response (9 complete responses and 25% partial responses) with no significant toxicity (49). Among those patients who responded to therapy, 43% survived 2+ years. Median survival among patients achieving a complete response was 42+ months. High baseline levels of circulating natural killer cells were the only prognostic factor that correlated with response. These results demonstrate that immunotherapy in combination with radical nephrectomy and adoptive transfer of TILs can provide substantial therapeutic benefit. Combined therapy with rIL-2, rIFN-α, and TILs has become the standard at the University of California at Los Angeles.

ALT. ALT refers to adoptive immunotherapy with autologous activated memory T lymphocytes that have been expanded and activated ex vivo. T lymphocytes are selected from peripheral blood leukocytes with anti-CD3 mAbs and then further enriched for activated memory T lymphocytes that have presumably been exposed to tumor antigens. These memory T cells are then expanded and non-specifically stimulated with cytokines to increase their cytokytic activity and multicytokine secretion. The resulting cell population presumably contains activated CTLs with potential antitumor activity. Early studies suggested that ALT in combination with cimetidine (an agent postulated to inhibit suppressor T-cell activity) produced a survival benefit (30).

To assess the clinical benefit of ALT in metastatic RCC, Dr. Michael Hawkins et al. randomized 90 patients to receive cimetidine monthly for 6 months, alone, or in combination with ALT (50). Median survival in the ALT group was >2 times longer (17 months) than in the group receiving cimetidine alone, a significant improvement. Ten of 45 patients (22%) survived 44+ months, and toxicity associated with ALT was minimal. A Phase III trial in which patients are randomized to rIFN-α plus cimetidine with or without ALT is currently underway.

Priming Tumor-specific CTLs. Animal models have shown that adoptive immunotherapy can be effective against advanced malignancies when lymphocytes derived from tumor-draining lymph nodes are primed with Corynebacterium parvum ex vivo and subsequently reinfused. Dr. Alfred Chang described clinical experiments involving patients with melanoma or RCC in which a portion of each patient’s tumor mass was excised and used to prime tumor-specific CTLs. Tumor cells were irradiated and mixed with T lymphocytes from draining lymph nodes that had been stimulated in culture with bacillus Calmette-Guérin. By doing so, it was hoped that tumor-specific CTLs would proliferate in culture. As many as 1011 cells, primarily CTLs, could then be reinfused into the patient. These cells demonstrate autologous antitumor cytolytic activity in vitro and have high GM-CSF and IFN-γ cytokine profiles, both of which are important for T-cell-mediated immune reactivity (62). In a recent clinical trial involving 12 patients with RCC, 2 complete responses and 2 partial responses were obtained with this treatment (51).

Dendritic Cells. Dendritic cells represent yet another potential tool for generating supercharged tumor-specific CTLs in culture. These potential antigen-presenting cells, found in bone marrow, lymph nodes, spleen, and skin, can now be propagated from peripheral blood mononuclear cells in cultures containing hematopoietic growth factors such as GM-CSF and rIL-4 (34). Dendritic cells express high levels of MHC class I and II antigens as well as a variety of cell surface costimulatory and adhesion molecules. Consequently, they present antigens effectively to T lymphocytes (63). In addition, dendritic cells produce some cytokines, including rIL-12 (35). Research in melanoma and prostate cancer has demonstrated the potential usefulness of dendritic cell cultures for generating an antitumor cellular immune response (64–66). Dendritic cells can be pulsed with tumor-specific peptide antigens, whole proteins, or RNA-encoding peptide antigens. Ongoing research is investigating the use of dendritic cells from cancer patients to optimize tumor antigen presentation in culture and to increase production of tumor-specific CTLs. Preliminary data presented by Dr. Peter Mulders indicate that this approach is applicable to the therapeutic induction of an RCC-specific immune response (33).

Gene Therapy

Genetically Engineered Tumor Cells. In an effort to stimulate a more potent antitumor immune response, researchers are experimenting with methods of increasing the immunogenicity of tumor cells in melanoma and RCC. One approach involves the introduction of MHC class I or cytokine genes into tumor cells to enhance tumor antigen presentation and activation of tumor-specific CTLs (67). Genetically engineered tumor cells can be irradiated and reinfused into the patient, where they will function as a vaccine.

Murine studies have demonstrated that GM-CSF is a potent stimulator of systemic antitumor immune responses (68). These findings
These results suggest that adoptive transfer of GM-CSF-secreting tumor infiltration by CD8 T cells may stimulate an effective antitumor response. Unfortunately, this methodology is expensive and labor intensive, which may limit its clinical application.

**Intralasional Gene Therapy.** The direct transfer of genes encoding MHC class I proteins or cytokines into tumor cells in vivo is a novel approach to enhancing the antitumor cellular immune response, as described by Dr. Alain Schreiber. One advantage of direct in vivo transfer of DNA into tumor cells compared with ex vivo transfer is the simplicity of the procedure, which does not require expensive and time-consuming manipulation of tumor cells in culture. One disadvantage may be the low efficiency of gene transfer. In vivo transfer of cytokine genes has been shown to reduce tumor growth in the RENCA murine model (69). The first Phase I clinical trial of in vivo intralasional gene transfer used cationic liposomes to deliver a plasmid harboring the IL-2 gene. No objective responses were observed; however, the procedure was demonstrated to be safe. The results of a dose-optimization trial are still pending.

Similar Phase I trials are currently underway to examine direct gene transfer of the HLA-B7 gene and the B2 microglobulin gene (70). The HLA-B7 gene was chosen for these studies because of evidence that it is involved in presentation of tumor-specific antigens in melanoma and RCC. Direct intralasional transfer of the HLA-B7 gene into melanoma tumors has produced clinical responses in some patients. However, to date, no clinical responses have been observed in RCC. The injection of the HLA-B7 gene into the tumors of 14 RCC patients by Dr. Nicholas Vogelzang and colleagues resulted in HLA-B7 RNA and protein expression in the majority of tumor samples. Although tumor infiltration by CD8+ T cells indicated induction of a cellular immune response, no clinical responses were observed (53). A recent Phase II study involving 25 patients has likewise failed to demonstrate clinical efficacy. These studies have indicated, however, the overall safety and feasibility of intralasional HLA-B7 gene transfer.

**Monoclonal Antibodies**

The role of mAbs in the treatment of metastatic RCC is evolving. mAbs that bind to tumor-specific antigens can be used for imaging or to deliver cytotoxic agents (i.e., toxins or radioisotopes) to the tumor with greater specificity than any other anticancer agent. Therapeutic mAbs have demonstrated clinical efficacy in colon cancer and non-Hodgkin's lymphoma (71, 72). In addition, mAbs are a powerful tool for identification of tumor antigens that may potentially be exploited as vaccines.

Recently, a RCC-specific antigen, the G250 antigen, was identified and has been cloned (73). The G250 antigen shows homology with a recently cloned cervical carcinoma-associated protein known as MN. Studies are underway to establish whether G250 is immunogenic and has potential for use as a RCC vaccine.

The anti-G250 mAb (mG250) is a murine immunoglobulin-G1 antibody that reacts with 85% of all RCC cell lines, all clear cell RCCs, and the majority of non-clear cell RCCs but does not react with normal kidney cells. According to Dr. Neil H. Bander, the 131I-labeled mG250 has considerable potential for imaging RCC and has proven to be more sensitive than conventional imaging techniques (74). The anti-G250 mAb may also have therapeutic potential. In a Phase II study investigating the therapeutic use of 131I-labeled mG250, 3 of 15 treated patients achieved a partial response (54). More recently, a chimeric (humanized) mG250 has been developed and is currently being tested in clinical trials to determine its therapeutic potential. The 131I-labeled chimeric mG250 has demonstrated a high level of tumor uptake with no immunogenicity (75). Therefore, it is a promising vehicle for delivery of cytotoxic levels of radiation to renal tumors.

**Tumor-specific Vaccines**

The first step in developing antitumor vaccines is the identification of RCC-specific tumor antigens that can also be used in vivo to generate CTLs with increased antitumor reactivity (76). Peptide mapping and mutagenesis techniques can then be brought to bear to enhance the immunogenicity of a putative tumor-associated antigen.

The G250 antigen was identified by generating mAbs to RCC cells and, Dr. Benoit van den Eynde et al. have also identified a putative RCC-specific antigen by expression cloning techniques. The antigen, designated RAGE for renal tumor antigen, stimulated autologous CTLs when expressed by transfected COS cells in the context of HLA-B7. Further analysis defined the antigenic peptide. Unfortunately, this RCC-specific renal tumor antigen is only expressed by approximately 2% of freshly isolated RCC tumors and approximately 40% of RCC cell lines. Therefore, its utility as a vaccine may be limited.

The identification of tumor-specific peptide antigens will play an important role in developing tumor vaccines but will require further study. The goals of this research are to elucidate the individual immune responses of cancer patients, identify tumor antigens, and isolate peptide antigens that will elicit a strong cellular immune response in the context of defined MHC class I antigens. Dr. Cornelius Melief described experiments examining the impact of the MHC class I binding stability on the immunogenicity of peptide antigens. The goal of this research is to define the parameters that define the most antigenic peptides (39).

**Therapeutic Challenges and the Host Immune Response**

Tumor physiology, multidrug resistance, and defects in the host immune response present challenges to successful therapy for RCC. On the third and final day of the symposium, Dr. Rakesh Jain presented an overview of renal tumor physiology and described factors such as heterogeneity in tumor blood flow, intratumor pressure, and leukocyte-endothelial interactions within tumor vasculature that may affect the efficacy of various therapeutic modalities. For example, factors that affect the ability of leukocytes to bind to tumor vascular endothelium and extravasate can complicate cell-mediated modalities. A better understanding of these factors could facilitate improvements in future therapeutic strategies.

Deficiencies in T-cell signaling may play a role in the poor antitumor immune response observed in mice bearing renal tumors. The relationship between functional deficits in the immune response and signaling molecules such as NF-kB was addressed by Dr. James Finke. One hypothesis is that renal tumors secrete soluble factors that inhibit the nuclear translocation of the RelA/NF-kB1 protein complex, which may lead to preclinical and clinical trials investigating the effectiveness of RCC cells genetically engineered to express GM-CSF in generating an anti-RCC immune response. This type of tumor cell vaccine has induced complete eradication of established tumors in mice. Dr. Jonathan W. Simons described a clinical study in which several RCC patients were injected with increasing numbers of GM-CSF-secreting tumor cells. An early infiltration of mononuclear cells (especially macrophages and dendritic cells) at the vaccination site and an increased delayed-type hypersensitivity response were observed in patients injected with untransfected and GM-CSF-transfected tumor cells. However, two of three patients injected with GM-CSF-secreting tumor cells exhibited a fourfold increase in the magnitude of the delayed-type hypersensitivity response compared with controls, and there was no evidence of toxicity (52). Furthermore, one of these patients exhibited a partial response to the vaccine. These results suggest that adoptive transfer of GM-CSF-secreting tumor cells may stimulate an effective antitumor response. Unfortunately, this methodology is expensive and labor intensive, which may limit its clinical application.

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may contribute to poor T-cell activation. This could explain the deficient IL-2 and IL-2 receptor α expression that has been observed in RCC tumor beds. Further research will be necessary to identify soluble factors responsible for this effect.

Conclusions

The successful treatment of metastatic RCC poses a significant therapeutic challenge. Because of the intrinsic multidrug resistance of renal cells, chemotherapy has proven ineffective. Immunotherapy with rIL-2 is the current standard for treating RCC, and a number of promising new immunotherapeutic strategies are currently under investigation. Although none have demonstrated clear superiority over rIL-2 therapy, some combination regimens and adoptive immunotherapy strategies may improve response rates and prolong survival with less morbidity than single-agent rIL-2 therapy. Reducing the toxicity of therapy is important, particularly for immunocompromised patients. Particularly promising are strategies to improve the antitumor activity of adoptively transferred leukocytes using cytokine priming, dendritic cells, or genetic manipulation. Research aimed at defining the clinical parameters that can predict responses to immunotherapy is also beginning to bear fruit.

Perhaps the most potent weapon that we can yield against RCC is a tumor vaccine that will mobilize an effective in vivo, cellular, antitumor, immune response. Currently, tumor cell vaccines using genetically altered tumor cells are in the early stages of clinical testing, and researchers are experimenting with direct intralesional delivery of the VHL gene detected in multiple microscopic clear cell renal lesions in von Hippel-Lindau disease patients. Am. J. Pathol., 149: 2090–2094, 1996.


References


