For decades, cancer vaccine investigations have generated much interest but little success. Now, however, these studies are finally beginning to bear fruit. Newer, more potent vaccines are producing specific immune responses in patients in clinical studies. Investigators are even seeing some clinical responses in these small clinical trials, which were designed simply to demonstrate immunogenicity or determine appropriate dosing strategies, not clinical efficacy.

“There are now several reports in the literature of complete responders,” said Howard L. Kaufman, MD. “It’s not common, but it is certainly amazing to see it in Phase I studies that may include only 10 or 20 patients.”

One critical development that fueled recent progress in cancer vaccine research was the recognition that specific proteins produced by tumors—the so-called tumor-associated antigens—can be used to vaccinate patients. Another key advance was the observation that dendritic cells are among the most potent cells available to stimulate the naïve immune system.

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A promising approach to cancer therapy is immunotherapy using dendritic cells. The major antigen-presenting cells in the body, dendritic cells transport specific tumor antigens to T-lymphocytes, which are then activated to destroy the tumor. Charles S. Hesdorffer, MB, ChB, and coworkers at Columbia Presbyterian Medical Center are in the vanguard of developing clinical applications for dendritic cell immunotherapy.

“The cells of the immune system may be functioning relatively normally in cancer patients, but nonetheless they exhibit certain deficiencies,” Dr. Hesdorffer stated. “For example, they may not recognize the correct tumor antigen, or they may not respond properly. By providing specific antigen peptides already bound to dendritic cells as a vaccine, these deficiencies might be overcome.”

The major disadvantage to this approach is that large amounts of peripheral blood mononuclear cells must be obtained from patients via leukophoresis. These cells must then be cultured for several days in the presence of a mix of growth cytokines, allowed to bind peptides, and then reinfused into the patient.

Direct injection of tumor antigen peptides into the patient is a much simpler procedure, but these peptides will be “picked up” by normal circulating dendritic cells and transported to T-cells. Because the tumor antigen is not specific, the response of the immune system will be too weak to destroy a large tumor—a major disadvantage of direct injection.

“It may be possible to overcome this barrier by debulking the tumor using prior surgery or radiation therapy,” said Dr. Hesdorffer. “On the other hand, direct injection of peptides might be an effective means of preventing development of certain types of cancer in patients who are at high risk for disease, including colon cancer and breast cancer.”

**A New Procedure**

The approach Dr. Hesdorffer is studying is to remove macrophages from the patient’s own blood and stimulate their development to dendritic cells using cytokines in the growth medium. The dendritic cells are then exposed to antigen and returned to the patient by intravenous or subcutaneous injection. Clinical studies using this approach are in the very early stages.

“Columbia University College of Physicians & Surgeons has developed and patented a closed system for the procedure, but a facility is still needed to work with more than a few patients at a time,” Dr. Hesdorffer said. Columbia Presbyterian Medical Center is develop-
A facility and methodologies for producing and working with these cells. One study is expected to include 20 patients with renal cell carcinoma, with the end point being activation of the immune system. Patients will be eligible only if they have 2 tumor antigens: HLAa2, which is the most common tumor antigen in kidney cancer patients, and HER-2nu, which is detected in 20% to 30% of patients. Another potential use of dendritic cell cancer vaccine is in an adjuvant setting for micrometastatic disease, especially since the vaccine may have synergistic activity with chemotherapy. Dr. Hesdorffer feels that the dendritic cell is an integral part of tumor immunology and the cornerstone of vaccine development. “Although clinical studies so far have been inadequate, this will change in the next 3 to 4 years,” he predicted.

Charles S. Hesdorffer, MB, ChB, is Director, Bone Marrow and Stem Cell Transplant Program and the Cellular Immunotherapy Research Program, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Associate Professor of Clinical Medicine, Columbia University College of Physicians & Surgeons. E-mail: hesdorffer@cancer-center.ccc.columbia.edu.

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Associate Professor of Surgery
Columbia University College of Physicians & Surgeons
hik2003@columbia.edu

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Co-Director of Cancer Prevention
NewYork-Presbyterian Hospital
Professor of Medicine and Epidemiology
Columbia University College of Physicians & Surgeons
ain1@columbia.edu

**Dattatreyudu Nori, MD**
Radiation Oncologist-in-Chief,
Department of Radiation Oncology
NewYork-Presbyterian Hospital
Professor of Clinical Radiology
Weill Medical College of Cornell University
dnori@nyp.org

**Peter B. Schiff, MD, PhD**
Director and Chairman,
Department of Radiation Oncology
NewYork-Presbyterian Hospital
Professor and Chairman,
Radiation Oncology
Columbia University College of Physicians & Surgeons
pbs1@columbia.edu

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NewYork-Presbyterian Hospital
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scw2004@med.cornell.edu

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Chief, Pediatric Oncology
NewYork-Presbyterian Hospital
Hettinger Professor of Clinical Pediatrics
Columbia University College of Physicians & Surgeons
mw216@columbia.edu

Web site: www.nypcancer.org
The technique of intensity-modulated radiation therapy (IMRT) has allowed radiation oncologists to deliver higher doses of radiation to diseased tissue than was possible with earlier generations of 3-D conformal radiation therapy (3D-CRT). Similarly, new advances in prostate brachytherapy have resulted in better outcomes for patients.

Now, researchers are eyeing an innovative imaging technology that could allow for the delivery of even higher radiation doses to targeted areas of the prostate gland. This new approach to prostate cancer radiotherapy, dubbed ultrasound tissue typing, is the result of a high-tech partnership between researchers at NewYork-Presbyterian Hospital and Columbia University College of Physicians & Surgeons, and Riverside Research Institute, a not-for-profit company with extensive experience developing imaging systems and technologies for the defense department.

“Right now, we treat the prostate gland as if it were all tumor,” said Peter B. Schiff, MD, PhD. “But with ultrasound tissue typing we can limit the volume of tissue receiving higher doses of radiation. This potentially makes treatment safer, but also allows us to go to even higher doses of radiation treatment with the expectation of better outcomes.”

“We are getting down not only to the organ or tissue level, but almost to the level of imaging clusters of tumor cells,” Dr. Schiff said. “We are not quite there yet, but we are getting close.”

Ultrasound tissue typing could become another valuable tool in the armamentarium of radiation oncologists at NewYork-Presbyterian Hospital, who already have at their disposal the most sophisticated technologies available.

The key component is IMRT, which unlike 3D-CRT allows the radiation oncologist to vary beam intensity across the treatment field according to a computer-generated treatment plan that takes into account thousands of possible treatment variations. The patient receives many small “beamlets” of varying intensity, rather than 1 large, uniform beam. The physician delivers a highly conformal dose distribution directed precisely at the tumor. Similar advances are occurring with brachytherapy procedures for selected prostate cancer patients.

Radiation oncologists familiar with IMRT say the modality appears to offer excellent local tumor control that results in less toxicity to surrounding healthy tissue. “Our early results indicate that our patients are enjoying a low risk of significant long-term complications,” said Dr. Schiff. The typical treatment regimen is 5 days per week for 9 weeks, or shorter if combined with other treatment modalities such as prostate brachytherapy or hormone therapy.

One thing is certain: IMRT will become increasingly integral to the prostate gland.
While intensity-modulated radiation therapy (IMRT) has tremendously advanced the precision of external beam radiation for prostate cancer, other technologic advances have also helped improve efficacy. For instance, a new ultrasound technology helps account for organ motion and biologic factors that can cause day-to-day variation in tumor location, thus reducing the risk of affecting nearby healthy tissue. The ultrasound system, known as BAT (B-mode acquisition and targeting), allows the physician to precisely account for day-to-day changes in prostate location. Dattatreyudu Nori, MD, FACP, noted that in one recent study of about 20 patients, use of the BAT system reduced the average geometric margin beyond the target tissue from 0.5 mm to 0.05 mm.

“The decrease in margins directly translates into less toxicity to normal structures in the vicinity of the prostate, including the rectum and bladder,” Dr. Nori said.

Brachytherapy, an alternative approach to the delivery of therapeutic radiation, has also become more precise. The implantation of radioactive pellets—a technology that Dr. Nori has been working to perfect for more than 25 years—is highly effective and relatively free of complications. The technique has advanced to the point where it is now an outpatient procedure.

“In the properly selected patient with early-stage disease we are seeing outstanding results, with a greater than 90% rate of cure and a very low rate of complications,” Dr. Nori reported.

As in IMRT, the precision of brachytherapy stems from a union of sophisticated imaging with computer analysis. Called conformal brachytherapy because the dose distribution conforms to the target being treated, a treatment strategy is based on 3-dimensional reconstruction of the prostate that is created from extensive computerized tomography and transrectal ultrasound. Computer analysis of the malignancy in relation to healthy tissue identifies the number of pellets to deliver, the number and angle and depth at which each needle should be placed. A custom template can then be designed to guide the needles based on the 3-D reconstruction of the target anatomy.

“Dr. Nori recommends combined IMRT and 3-D conformal brachytherapy treatment in high-risk patients, citing published data from NewYork-Presbyterian Hospital showing a significant improvement in results compared with single-modality treatment. At NewYork-Presbyterian Hospital, staging and risk stratification of prostate cancer has been employed to guide candidates for radiation to either brachytherapy or IMRT alone or in combination.

However, more recently, a substantial proportion of high-risk patients has begun to receive both. “Brachytherapy can provide a very precisely delivered dose escalation with a low risk of additional morbidity,” said Dr. Nori, noting the rationale for using the combination in high-risk patients. “Conformal brachytherapy is effective, is associated with relatively low cost, and is well accepted by patients.”

Dattatreyudu Nori, MD, FACP, is Radiation Oncologist-in-Chief, Department of Radiation Oncology, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Professor of Clinical Radiology, Weill Medical College of Cornell University. E-mail: dnori@nyp.org.

Peter B. Schiff, MD, PhD, is Director and Chairman of Radiation Oncology, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Professor and Chairman, Department of Radiation Oncology, Columbia University College of Physicians & Surgeons. E-mail: pbs1@columbia.edu.
work confirming that taxanes are active in prostate cancer. According to Daniel P. Petrylak, MD, the senior author of the Phase III trial, activity observed in Phase II trials at Columbia Presbyterian Medical Center provided the impetus to move to a trial that is involving centers across the country.

“Previous chemotherapy, such as the combination of prednisone and mitoxantrone, has had significant palliative effects on bone pain but it has not meaningfully extended survival,” Dr. Petrylak noted. “The combination of estramustine phosphate with the taxanes paclitaxel or docetaxel produces greater than additive cytotoxicity in vivo, and Phase I and II studies of taxane-based therapy have been demonstrating improved survival in hormone-refractory prostate cancer compared to historical controls.”

In the Phase III trial, which includes both overall survival and disease-free survival as endpoints, 750 patients have been entered and results are expected in about one year. The taxane-based therapy has the potential to become the new standard if results are favorable, but this is just one avenue of clinical trial work being performed. Dr. Petrylak, who is also active in evaluating novel therapies, hopes that taxane-based therapies will be a foundation on which to make inroads in advanced prostate malignancy. The goal is not only to extend lives but also to improve the quality of those lives.

Prostate-Specific Membrane Antigen

In efforts to convert advanced, terminal prostate cancer to a survivable disease, a team of investigators at NewYork Weill Cornell Medical Center are moving forward with new forms of immune therapy. The goal is to move beyond androgen replacement, which often leads to hormone-refractory disease and exhaustion of therapeutic options. Immune therapies based on monoclonal antibodies have been made possible by a series of recent advances in understanding the molecular biology of prostate cancer.

One of the most promising targets of monoclonal antibodies is prostate-specific membrane antigen (PSMA), a membrane protein that is a marker of prostate cancer and has been intensively studied since the late 1980s. PSMA is of special interest in prostate cancer patients because it is highly expressed and is up-regulated by androgen deprivation. Monoclonal antibody to PSMA targets both the primary tumor and metastatic cancer cells. A research group led by Neil Bander, MD, has developed 4 different anti-PSMA monoclonal antibodies. These antibodies are the first to bind the extracellular domain of PSMA on viable prostate cancer cells. After binding, the antibodies are internalized, offering an attractive method of specifically targeting the delivery of tumor toxins, radioisotopes, or drugs. The prototype anti-PSMA antibody, called J591, has been deimmunized, a next-generation form of monoclonal antibody humanization that renders the antibody non-immunogenic in patients and thereby allows multiple-dose regimens.

Investigators at NewYork Weill Cornell Medical Center are also performing research into the targeting of prostate cancer metastases in bone and solid organs with monoclonal antibodies. According to David Nanus, MD, this work will provide valuable information for future studies in larger patient populations, and will hopefully lead to better diagnosis and treatment of advanced prostate cancer.

Drs. Nanus and Bander and coworkers, including Matt Milowsky, MD, are conducting 2 Phase I dose-escalation radioimmunotherapy trials with 90yttrium- and 177lutetium-labeled J591. Several responses were seen in patients with advanced prostate cancer. Two patients receiving 90yttrium-labeled J591 had prostate-specific antigen declines of 65% to 85% and measurable objective responses, with several additional responses seen in patients receiving 177lutetium-labeled J591. The most common toxic effect of the treatment has been reversible thrombocytopenia, which increased in incidence with higher doses.
of radiolabeled antibody. These studies additionally suggest that imaging using radioisotopes attached to monoclonal antibodies is as good as if not better than standard imaging techniques for detecting metastatic prostate cancer cells.

In another Phase I dose-escalation study at NewYork Weill Cornell Medical Center, Dr. Nanus and his colleagues are evaluating whether J591 antibody binds to vascular endothelial cells of other solid tumor types in patients. Preclinical studies show that J591 antibody binds to vascular endothelial cells found in a variety of solid tumors but not to benign endothelium. Eligible patients have refractory solid tumor malignancies whose tumor types express PSMA on the neovasculature. Twenty patients have been treated with $^{111}$indium-labeled J591 at a dose ranging from 5 mg to 40 mg. Localization of the antibody to tumor sites was seen in 15 of the 20 patients. Although there were no objective responses, 1 patient with colon cancer had a 50% decline in carcinoembryonic antigen (CEA), 2 patients had less pain and an improved performance status, and 2 patients with progressing kidney cancer have had stable disease for over 6 months.

Neil Bander, MD, is Attending Urologist, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Professor of Urology and Urological Oncology at Weill Medical College of Cornell University. E-mail: nhbander@med.cornell.edu.

David Nanus, MD, is Attending Urologist, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Associate Professor of Medicine and Urology at Weill Medical College of Cornell University. E-mail: dnanus@med.cornell.edu.

Daniel P. Petrylak, MD, is Director, Genitourinary Oncology Program, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Associate Professor of Medicine, Columbia University College of Physicians & Surgeons. E-mail: dpp5@columbia.edu.

## Surgical Innovations Target Quality of Life

Individualization of care takes precedence over the numerous surgical innovations for prostate cancer pioneered or advanced at NewYork-Presbyterian Hospital. For example, robotic laparoscopy has been successfully integrated into the pool of surgical approaches, but this innovation is offered selectively according to its potential advantages.

“There are clearly patients, such as the obese, who are not good candidates for laparoscopy, whether or not a robotic approach is used,” observed Carl Olsson, MD. “The opportunity for improving outcome with the newer surgical approaches really depends on recognizing which patients are likely to benefit.”

Peter Schlegel, MD, concurred. His team, among the first to introduce laparoscopy in the New York area, has also integrated robotic laparoscopy into the care of selected patients with prostate cancer. However, it is their understanding of urogenital anatomy that he credits for the greatest opportunity for improvement in outcome. He has been active in developing nerve-sparing removal of prostate and bladder malignancies to preserve continence and potency.

“The real advances in surgery are generated by our better understanding of the anatomical structures around the prostate and their enervation. This involves surgery designed to better spare these structures. Newer techniques for surgical reconstruction also help to maintain function after excision is performed,” Dr. Schlegel observed.

The large volume of cases at NewYork-Presbyterian Hospital helps hone technical skill. At Columbia Presbyterian Medical Center alone, more than 400 prostate cancer surgeries are performed each year, according to Dr. Olsson. With such a large volume and an emphasis on individualization of care, surgeons maintain skills with a variety of approaches selected to best suit the patient.

Not least important to the patient has been the clinical pathway developed at NewYork Weill Cornell Medical Center to speed patient recovery. According to Dr. Schlegel, the team approach to optimizing analgesia and circumventing its side effects has cut hospital stay almost in half, reducing average stays from 4 to 5 days to 2 to 3 days. More rapid discharge is achieved by diminishing the incidence of nausea, constipation, and other risks of analgesia.

“This streamlined approach to recovery has been used in other cancers, but we are one of the first to apply it in prostatectomy,” Dr. Schlegel reported. “Patients are rendered more comfortable more quickly, and I think it is a meaningful improvement in their experience.”

As a leading national center in prostate cancer surgery, NewYork-Presbyterian Hospital has provided ample opportunity to apply innovations in care, but both Dr. Olsson and Dr. Schlegel emphasized that innovations are applied selectively and only when they yield an opportunity for an improvement in outcome. The full spectrum of surgical options is brought to bear on the goal of achieving cancer-free margins while preserving functions that define postsurgical quality of life.

Carl Olsson, MD, is Attending Urologist, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and John K. Lattimer Professor and Chairman of the Department of Urology, Columbia University College of Physicians & Surgeons. E-mail is cao2@columbia.edu.

Peter Schlegel, MD, is Associate Attending Urologist, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Acting Chairman of Urology and Associate Professor of Urology and Reproductive Medicine, Weill Medical College of Cornell University. E-mail: pnschleg@med.cornell.edu.
Lung cancer survival rates remain dismal, largely because the disease is most often diagnosed in advanced stages. One hope for a cure is catching the disease early, when interventions can make a marked difference.

That’s the focus of ongoing research projects led by New York Weill Cornell Medical Center. Investigators are evaluating low-radiation dose computed tomography (low-dose CT) to detect early stage lung cancer in high-risk individuals. So far, the results have been encouraging.

“CT screening promises to transform the prognosis for lung cancer, just as mammography did for breast cancer, and the Pap test did for cervical cancer,” said Claudia I. Henschke, MD, PhD.

Preliminary findings of the landmark Early Lung Cancer Action Project (ELCAP) have provided evidence that lung cancer screening may help save the lives of high-risk individuals. Dr. Henschke and colleagues published results from ELCAP (Lancet 1999; 354[9173]:99-105) showing that low-dose CT screening greatly improved detection of small nodules at an earlier and potentially more curable stage in more than 1,000 symptom-free volunteers over age 60 with a smoking history of at least 10 pack-years. A subsequent report (Cancer 2001;92[1]:153-159) suggests that low-dose CT screening allows for diagnosis at a substantially earlier, more curable stage.

False-positive screening test results were very uncommon, investigators reported. Conventional X-rays did not reveal 79% of the early stage cancers seen on CT scan. Of the CT-detected cancers, 96% could be removed surgically; by comparison, lung tumors detected in usual clinical practice today can be removed in fewer than half of all cases.

Among 1,184 repeat screenings of 841 high-risk individuals, investigators detected new pulmonary nodules with interim growth in 30 cases, or 2.5%. Of that set of positive test results, 2 patients died of unrelated causes, and the new nodules resolved in another 12 cases. For the remaining 16 cases, investigators documented further growth in 8. Biopsies showed malignancies in 7 cases, of which 6 were non-small cell carcinomas, and all were resectable.

By comparison, investigators noted a curability rate of greater than 80% for early stage, non-small cell malignancies detected by CT, compared with an overall survival rate of only 16% for non-small cell carcinoma of the lung in the general population.

One question is whether routine lung cancer screening for high-risk patients will be cost-effective. Data from this study suggest the cost per life year saved could be as low as $10,000, according to investigators, which is “well below that for existing screening programs for breast carcinoma or cervical carcinoma and is well below the benchmark of $50,000 used in the US,” they stated.

The newer studies will help answer key questions, such as the impact of different diagnostic techniques and the benefit of treating early lung cancers.

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Low-dose CT screening at NY-ELCAP greatly improves detection of small nodules at an earlier and more curable stage.
It is important to demonstrate not only whether lung cancer screening is effective, but also cost-effective.

side of New York and in other countries. In the first phase of I-ELCAP, investigators will evaluate the usefulness of CT screening for identifying early stage lung carcinomas. In the second phase, they will evaluate how survival after early intervention compares with survival after the typical late intervention.

Dr. Henschke, who serves as principal investigator for I-ELCAP, said this project will not only help assess the method of early diagnosis, but the extent to which early malignancies are curable by early resection, and which are fatal without early resection.

“We are providing screening to high-risk people, and we already know with the data to date we will save lives by doing that,” Dr. Henschke explained. “Their participation will help us quantify how many lives can be saved and at what cost.”

John Austin, MD, is Director of Thoracic Imaging, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Professor of Radiology, Columbia University College of Physicians & Surgeons. E-mail: jha3@columbia.edu.

Claudia I. Henschke, MD, PhD, is Chief of the Division of Chest Imaging, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Professor of Radiology, Weill Medical College of Cornell University. E-mail: chensch@med.cornell.edu.

More information on lung cancer screening initiatives can be found by visiting www.nyelcap.org and www.ielcap.org. The telephone number for NY-ELCAP is (212) 305-6849.

Side Effects Reduced in Use of IL-2 for Melanoma

A major problem hindering greater use of interleukin-2 (IL-2) for melanoma therapy is the lack of awareness among community oncologists of the efficacy of the agent as well as the relatively low incidence and severity of its side effects, when compared to 10 years ago.

“I absolutely believe that the future of IL-2 cancer therapy looks bright,” observed Howard Kaufman, MD. “On the one hand, the problem of toxicity is minimal today. In the future, we hope to see more widespread use of IL-2 for other types of cancer, for different diseases—including HIV infection, and in combination with vaccines.”

While early-stage malignant melanoma is curable, the prognosis in metastatic disease is poor. Since the natural history of the disease suggests the possible role of the immune system, various immunostimulating agents have been evaluated, but these have failed to demonstrate efficacy. More recently, recombinant interferon alfa has shown some clinical activity.

In a Phase III trial in advanced melanoma, Eton et al (J Clin Oncol 2001;20:2045-2052) compared the effects of chemotherapy using the standard regimen of cisplatin, vinblastine, and dacarbazine with those of sequential biochemotherapy consisting of the same regimen plus IL-2 and interferon alfa-2b. Biochemotherapy was statistically superior to chemotherapy, both in response rate and time to progression (TTP), and there was an improvement in overall survival in the biochemotherapy group. However, biochemotherapy produced substantially more constitutional, hemodynamic, and myelosuppressive toxic effects. Furthermore, a larger cooperative group trial has recently been completed and did not support the use of biochemotherapy.

Dr. Kaufman is one of a team of medical and surgical oncologists who are working together to enhance the safety of IL-2 for treating cancer. Dr. Kaufman and his coworkers are minimizing the incidence and severity of the major toxicities—ie, infection and cardiotoxicity—by using prophylactic cardioprotective agents and antibiotics. In an ongoing study, patients at Columbia Presbyterian Medical Center are receiving high-dose IL-2 every 8 hours for up to 15 doses. After 2 weeks of rest, the cycle is repeated. In responding patients dramatic and long-lasting responses have been seen, including an 8-year-old girl with ocular melanoma and liver metastases. Dr. Kaufman noted that a core group of nurses and physicians at Columbia Presbyterian Medical Center undergo training at the National Cancer Institute to provide them with state-of-the-art skills in proper management of cancer patients undergoing IL-2 therapy, and that this multidisciplinary approach will result in safer treatment.

John Austin, MD, is Director of Thoracic Imaging, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Professor of Radiology, Columbia University College of Physicians & Surgeons. E-mail: jha3@columbia.edu.

Claudia I. Henschke, MD, PhD, is Chief of the Division of Chest Imaging, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Professor of Radiology, Weill Medical College of Cornell University. E-mail: chensch@med.cornell.edu.

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John Austin, MD, is Director of Thoracic Imaging, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Professor of Radiology, Columbia University College of Physicians & Surgeons. E-mail: jha3@columbia.edu.

Claudia I. Henschke, MD, PhD, is Chief of the Division of Chest Imaging, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Professor of Radiology, Weill Medical College of Cornell University. E-mail: chensch@med.cornell.edu.

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New immunotherapeutic approaches have demonstrated clinical activity in the treatment of lymphomas. Now, investigators are going a step further with new strategies that could improve response rates while reducing toxicity.

One intriguing new approach is to use 2 monoclonal antibody treatments with different mechanisms of action, according to John P. Leonard, MD.

“By combining antibodies, we hope to see better therapeutic results with less toxicity than chemotherapy,” said Dr. Leonard. “In fact, patients are often very interested in this approach in order to try to avoid treatment with chemotherapy.”

In one study currently under way, Dr. Leonard, together with Morton Coleman, MD, and colleagues, is looking at the combination of 2 immunotherapies: rituximab, a chimeric anti-CD20 antibody proven to have significant antitumor effects, and a newer agent known as epratuzumab, which binds to the CD22 antigen.

This pilot study, which so far includes 21 patients with relapsed low-grade or aggressive non-Hodgkin’s lymphoma (NHL), is one of over 15 open immunotherapy trials that Dr. Leonard and colleagues are currently undertaking. In the past 4 years, more than 400 patients have entered such trials through Weill Medical College of Cornell University and NewYork-Presbyterian Hospital.

Preliminary response data suggest that rituximab (in a standard dose of 360 mg/m² I.V.) followed by epratuzumab (375 mg/m² I.V.), given weekly for 4 doses, was generally well tolerated and resulted in significant tumor responses in most patients.

“The results are early, and the numbers are small, but we are very enthusiastic,” Dr. Leonard said. “In fact, the majority of these appear to be complete responses, which are generally better and thus far more durable than one would expect with rituximab alone.”

According to data presented at the 2002 meeting of the American Society of Clinical Oncology and recently updated, 13 of 20 evaluable patients had an objective response, including 3 responses (1 partial, 2 complete) in 3 patients with diffuse large B-cell NHL, and 10 responses in 16 patients with indolent NHL (56% complete response, 6% partial). The majority of these responses are ongoing with more than 13 months of follow-up at press time. All of these patients had progressive disease after prior chemotherapy regimens, including autologous stem cell transplant in some cases.

Toxicity was similar to that seen with rituximab alone, and all infusion-related toxicities were of NCI grade 1-2. Investigators are now conducting a follow-up multicenter trial.

Investigators have also extensively studied radiolabeled antibodies. Trials of these radioimmunoconjugates, which have the potential added benefit of targeting radiation to the tumor, suggest improved activity, albeit with somewhat increased toxicity, particularly to the bone marrow, according to Dr. Leonard. In general, however, the side effects of these treatments compare quite favorably to chemotherapy. Yet another new approach is using vaccines that recognize unique antigens on lymphoma cells. Investigators at Weill Medical College of Cornell University and NewYork-Presbyterian Hospital have participated in a number of clinical trials of these vaccines.

“Clearly, these agents have a potential role as novel therapeutic agents for lymphoma,” Dr. Leonard said. “We are very pleased to offer to patients these new treatment options that can be quite effective and well tolerated. In addition to providing alternative treatment possibilities, we are hopeful that these promising regimens will ultimately improve outcomes for lymphoma patients.”

John P. Leonard, MD, is Medical Director of Oncology Services and Clinical Director of the Center for Lymphoma and Myeloma, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Assistant Professor of Medicine, Weill Medical College of Cornell University. E-mail: jpleonar@med.cornell.edu.
Both of these approaches have been combined in a series of vaccine clinical trials under way at Columbia University College of Physicians & Surgeons. One trial looks at tumor expression of NY-ESO-1, a tumor-associated antigen made by many tumor types that appears to be particularly immunogenic.

“There is some evidence to show peptides derived from NY-ESO-1 ultimately cause antibody production,” said Kyriakos Papadopoulos, MD. “The potential is to get a cell-mediated response, but also to mobilize the humoral arm of the immune system.” Thus, NY-ESO-1 appears to elicit both antibody-mediated immunity as well as cell-mediated (T-cell) immunity.

In this trial, investigators are enrolling 15 patients with advanced tumors, in particular sarcomas, which express NY-ESO-1. Patients receive a vaccine containing NY-ESO-1 peptide along with an adjuvant cytokine GM-CSF. A second trial in patients with melanoma incorporates 4 tumor-associated antigens including NY-ESO-1.

NY-ESO-1, today considered a model antigen for vaccine development, was discovered and first reported in 1997 by researchers with Weill Medical College of Cornell University and the Ludwig Institute for Cancer Research, New York Branch. The Ludwig Institute, a global not-for-profit research organization, and the Cancer Research Institute have formed academic affiliations with researchers at NewYork-Presbyterian Hospital to study this and other immunotherapeutic strategies.

Preliminary data from a recent study suggests NY-ESO-1 vaccines may be particularly promising in lung cancer. Administering the peptides, again with GM-CSF as an adjuvant, is safe and induced a peptide-specific T-cell reactivity in some of the first patients treated, according to investigator Nasser Altorki, MD.

“If immunotherapy works, then there is a whole new avenue to control the balance between the host and the cancer,” said Dr. Altorki. “Just as hypertensives live a long life if they control their blood pressure, cancer patients could also live a long time, not necessarily by eradicating the disease, but by coexisting with it.”

Dr. Altorki is also looking for immunologic responses in patients who are exposed to another well-characterized tumor-associated antigen, MAGE-3. This and the NY-ESO-1 antigens are 2 of the 20 or so cancer-testes (CT) antigens that have thus far been identified. These antigens are present in cancers, but not in most normal tissue, making them ideal targets.

Costimulatory Molecules

Beyond stimulatory cytokines, recent clinical focus has been on the so-called costimulatory molecules, which may enhance T-cell responses to tumor-associated antigens. “We are able to manipulate these responses in very sophisticated ways now,” said Dr. Kaufman.

In studies of vaccines using poxviruses expressing carcino-embryonic antigen (CEA) but no costimulatory molecule, Dr. Kaufman and colleagues found about one third of patients with CEA-expressing tumors exhibited a T-cell response but no clinical response. However, with the addition of a single costimulatory molecule, that same one third of patients also had clinical responses.

Investigators pooled that data with results from a similar, separate study conducted elsewhere. In the 77-patient analysis, survival was doubled for those who exhibited a T-cell response (20 months versus 10 months).

More recently, Dr. Kaufman and colleagues have found that combining 3 costimulatory molecules provides superior T-cell activation. “As we understand how to get better immune responses we are going to be able to fine-tune these vectors and apply them to a wide range of diseases.”

Adoptive Immunotherapy

Another intriguing recent concept is “adoptive immunotherapy,” or the use of agents that allow the body to define its own immune process, which is then enhanced artificially outside the body.

“Onece patients have developed their own immune reactivity to the tumor—via specific clones of T-cells—we will try to remove some of these clones, grow them, and give them back in very...
large numbers to the patients,” Charles S. Hesdorffer, MB, said. “This could be a very powerful, selective approach to killing off any residual tumor cells.”

Researchers at Columbia University College of Physicians & Surgeons will be applying novel adoptive immunotherapy techniques to patients in vaccine studies of breast, lymphoma, and other cancers. “Now that we know more about how the immune system works, we can focus on the right cells to do the job,” Dr. Hesdorffer said. “In the past, it had always been somewhat of a mystery, but now, we are starting to get to the nitty-gritty of how the process works, and therefore can potentially do something for patients.”

Nasser Altorki, MD, is Director, Division of Thoracic Surgery, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Professor of Cardiothoracic Surgery, Weill Medical College of Cornell University. E-mail: atb2002@med.cornell.edu.

Charles S. Hesdorffer, MB, CHB, is Director, Bone Marrow and Stem Cell Transplant Program and the Cellular Immunotherapy Research Program, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Associate Professor of Clinical Medicine, Columbia University College of Physicians & Surgeons. E-mail: hesdorffer@cancercenter.ccc.columbia.edu.

Howard L. Kaufman, MD, is Associate Director of the Herbert Irving Comprehensive Cancer Center and Attending Physician, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Vice Chairman of Surgical Oncology and Associate Professor of Surgery, Columbia University College of Physicians & Surgeons. E-mail: hlk2003@columbia.edu.

Kyriakos Papadopoulos, MD, is Assistant Attending Physician, Division of Medical Oncology, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Assistant Professor of Medicine, Columbia University College of Physicians & Surgeons. E-mail: kpp6@columbia.edu.

The highly immunogenic NY-ESO-1 antigen, discovered by researchers at Weill Medical College of Cornell University and a prominent New York-based research organization, has become a promising target for vaccine development.