

NEW YORK-PRESBYTERIAN Oncology

Premiere Issue
2002

Affiliated with COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS & SURGEONS and WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

Perfecting the Whipple Procedure

The Whipple procedure for pancreatic cancer was developed by researchers at Columbia University College of Physicians & Surgeons. At NewYork-Presbyterian Hospital, the goal is now cure, not palliation, and the proportion of patients surviving pancreatic cancer is creeping upward. Recent innovations, including more sophisticated perioperative management and the use of laparoscopic approaches to confirm the need for open resection, have lowered surgical mortality rates to a fraction of those reported nationally. In addition, a comprehensive preoperative evaluation has essentially eliminated surprises during resection.

The simple explanation for the very low rate of mortality is the experience drawn from more than 100 combined

see Whipple, page 10

Bone Marrow and Stem Cell Transplantation: The Art Advances

Rigorous criteria are used to select transplant centers for the National Marrow Donor Program (NMDP). As testament to their leadership in bone marrow and stem cell transplantation, both centers of NewYork-Presbyterian Hospital have been so designated. NewYork Weill Cornell Medical Center is distinguished as a transplant center as well as a stem cell and bone marrow collection center for the NMDP. Morgan Stanley Children's Hospital of NewYork-Presbyterian, located at Columbia Presbyterian Medical Center, is also an approved NMDP Unrelated Stem Cell Transplant Center. Both centers are engaged in active research programs and attract large numbers of patient referrals from throughout the tri-state metropolitan area—indeed, from throughout the country and the world.

INNOVATIONS FOR ONCOLOGISTS

NewYork Weill Cornell Medical Center Programs

Michael W. Schuster, MD, Director of Adult Bone Marrow and Stem Cell Transplantation, outlined several ongoing studies in bone marrow and stem cell transplantation at NewYork Weill Cornell. Five novel trials are particularly noteworthy:

see NMDP Centers, page 11



Michael W. Schuster, MD, and colleagues are pioneering new technologies to treat hematologic malignancies.

INSIDE

Gamma Knife Radiosurgery

2 Stereotactic radiosurgery with the innovative Gamma Knife is only the latest radiosurgical advancement available.

Phase I Pediatric Clinical Trials

4 A look at the only hospital in the tri-state area to be selected to receive Phase I contract grants from the NCI.

Antiangiogenics vs. Leukemia

7 Researchers have begun to identify ways to combat acute myeloid leukemia with antiangiogenic drugs.

Gamma Knife Latest Stereotactic Radiosurgical Procedure

For over a decade, our center has been at the forefront of the various stereotactic technologies,” said Steven Isaacson, MD, Co-Director, The Center for Radiosurgery, Department of Radiation Oncology, at Columbia Presbyterian Medical Center. (Michael Sisti, MD, is the center’s other Co-Director.) As a result, NewYork-Presbyterian Hospital offers a full spectrum of stereotactic radiosurgical procedures.

The major advantage of noninvasive radiosurgery techniques is the ability to target lesions in the brain while minimizing radiation exposure to normal tissues. This leads to fewer post-treatment complications and shorter

hospital stays. “We can deliver radiation as precisely as surgery at our center of excellence,” said Dr. Isaacson.

Among the benefits of Gamma Knife radiosurgery are its precision and safety, which lead to reduced post-treatment complications and shorter hospital stays, and enable treating areas of the brain that could not otherwise be treated with conventional surgery or other techniques.

Physicians have access to the Gamma Knife, located at the Center for Radiosurgery, as well as other stereotactic treatments that are offered at both NewYork Weill Cornell and Columbia Presbyterian Medical Centers. These include Linear Accelerator-Based Stereotactic Radiosurgery, which is suitable for larger targets, and 3-D Conformal Intensity Modulated Radiation Therapy (IMRT), appropriate for large, irregularly shaped lesions. Theodore Schwartz, MD, Director of the Center for Epilepsy and Brain Tumor Surgery, NewYork Weill Cornell Medical Center, performs Gamma Knife procedures at Columbia Presbyterian Medical Center.

Patient care delivered by the Center for Radiosurgery involves a multidisciplinary effort on the part of radiation oncologists, neurosurgeons, medical oncologists, neurologists, neuroradiologists, and medical physicists. “The collaboration between Columbia Presbyterian Medical Center and NewYork Weill Cornell Medical Center demonstrates the ongoing cordial and



Steven Isaacson, MD, and Michael Sisti, MD, review imaging studies.

productive relationship between the two campuses,” Dr. Isaacson noted.

The Procedure

Stereotactic radiosurgical procedures involve several steps, explained Peter Schiff, MD, PhD, Director and Chairman of Radiation Oncology at Columbia Presbyterian Medical Center. On the day of surgery, the patient has a stereotactic headframe placed, which allows for precise localization of the abnormality and provides a reference for imaging and treatment throughout the procedure. Imaging studies are performed (e.g., CT scan, MRI, angiogram), and the team reviews the computerized images to plan the course of treatment.

Once the team establishes the target area of the brain and an appropriate radiation dosage, the patient undergoing Gamma Knife radiosurgery lies down with his or her head secured in the stereotactic frame, which is positioned inside a large metal collimator. The collimator will direct the system’s radiation to predetermined sites in the patient’s

Precision Targeting

Lesions treated by the Gamma Knife:

- vascular lesions such as arteriovenous malformations
- acoustic neuromas
- meningiomas
- pituitary tumors
- pineal tumors
- metastases
- glial and astrocytic tumors
- skull base tumors
- other benign and malignant tumors
- trigeminal neuralgia
- Parkinson’s disease

Other Stereotactic Techniques

The Center for Radiosurgery at Columbia Presbyterian and the Department of Radiation Oncology at New York Weill Cornell offer two other types of noninvasive precision radiation treatments, each appropriate for specific types of brain abnormalities. Both employ stereotactic methodology for highly accurate three-dimensional targeting.

- Linear Accelerator-Based Stereotactic Radiosurgery is suitable for larger targets. This technology provides radiation in the form of a single, highly focused beam applied in multiple sweeps around the brain lesion. This method also allows multiple smaller-dose, or fractionated, stereotactic radiotherapy, which is advantageous in selected patients.
- 3-D Conformal Intensity Modulated Radiation Therapy (IMRT) is favored for larger, irregularly shaped lesions surrounded by healthy tissue that is especially sensitive to radiation. This system, which can also be given with fractionation, employs beam-intensity modulation technology that shapes the radiation to conform to the target site.

brain. Next, the patient slides into the Gamma Knife's sphere containing the radiation sources.

Treatment usually consists of a series of 10-minute exposures. Little or no discomfort is associated with the Gamma Knife procedure, and overnight hospitalization is not usually required.

Gamma Knife surgery is an appropriate technique for both adults and pediatric patients with deep-seated brain lesions.

Since 1998, when the Gamma Knife first became available at the Center for Radiosurgery, 935 patients have been treated using this technique. Ongoing research and development continues to expand the applications of the Gamma Knife, Dr. Isaacson said.

The Center for Radiosurgery can be reached at (877) PH GAMMA

Dr. Isaacson can be reached at sri1@columbia.edu

Dr. Schiff can be reached at pbs1@columbia.edu

Dr. Schwartz can be reached at schwarh@med.cornell.edu

New York-Presbyterian Oncology is a publication of the Cancer Centers of New York-Presbyterian Hospital. The Cancer Centers are at the forefront of cancer screening and diagnosis, and basic science and clinical research. The Cancer Centers serve over 6,500 new cancer patients each year, who receive state-of-the-art multidisciplinary care. The Cancer Centers include the Herbert Irving Comprehensive Cancer Center at Columbia Presbyterian Medical Center and the New York Weill Cornell Cancer Center, which are respectively comprised of physicians from the Columbia University College of Physicians & Surgeons and the Weill Medical College of Cornell University.

New York-Presbyterian Oncology Editorial Board:

COLUMBIA PRESBYTERIAN MEDICAL CENTER

Karen Antman, MD

Chief, Division of Medical Oncology

Director, Herbert Irving Comprehensive Cancer Center

Alfred I. Neugut, MD, PhD

Co-Director of Cancer Prevention

Peter B. Schiff, MD, PhD

Chairman, Department of Radiation Oncology

Director, Radiation Oncology Service

Daniel H. Smith, MD

Associate Attending, Division of Obstetrics & Gynecology

Michael Weiner, MD

Chief, Pediatric Oncology

NEW YORK WEILL CORNELL MEDICAL CENTER

John M. Daly, MD

Chairman and Surgeon-in-Chief, Department of Surgery

Andrew J. Dannenberg, MD

Co-Director of Cancer Prevention

Dattatreya Nori, MD

Radiation Oncologist-in-Chief

Roy L. Silverstein, MD

Chief of Hematology and Medical Oncology

Alexander J. Swistel, MD

Director, Weill Cornell Breast Center

Website: www.nypcancer.org

Therapeutic Innovations Offered In Phase I Pediatric Clinical Trials

The only metropolitan hospital in the tri-state area to be selected to participate in Phase I pediatric clinical trials of novel therapeutics by the Children's Oncology Group (COG) is Morgan Stanley Children's Hospital of NewYork-Presbyterian, located at Columbia Presbyterian Medical Center. According to Michael A. Weiner, MD, Chief of Pediatric Oncology, Herbert Irving Child & Adolescent Oncology Center, only 20 Phase I contract grants have been awarded by the National Cancer Institute through the auspices of the COG consortium.

In 2001, the Pediatric Oncology Group and the Children's Cancer Group joined forces under one umbrella group—the Children's Oncology Group. Prior to this reorganization, both groups competed for pediatric patients for clinical trials.

"Being selected as one of the participating centers in the consortium is a feather in our cap, and it recognizes our pediatric oncology program as one of the elite institutions in the country," Dr. Weiner stated.

Traditionally, children have been excluded from clinical trials of experimental therapeutics. But this situation has gradually changed as a result of efforts by lobbyists for patients, families and physicians.

Childhood Cancers Rare

It can be difficult to recruit children for clinical trials due to the smaller pool of children with cancer compared with adults. Childhood cancers account for 12,000 new diagnoses each year. There are 850 adults with cancer per 100,000 people as compared to only 15 children with cancer per 100,000.

Although childhood cancers have a high cure rate, ranging from 60% to 65%, this still leaves 35% to 40% of children with cancer who are not cured.

"The clinical trial program offered through the COG consortium will provide Columbia Presbyterian's refractory patients with the most cutting-edge approaches," Dr. Weiner emphasized. "We look upon this as an opportunity not only to provide access to new therapies for our own patients but also to attract referrals from the tri-state area and elsewhere."

Highlights of the COG Phase I Program

Mitchell S. Cairo, MD, the principal investigator of the Phase I/II Developmental Therapeutic Grant, is also Director, Pediatric Cancer Research Program, and Director, Developmental Therapeutics and Hematopoiesis, Morgan Stanley Children's Hospital of NewYork-Presbyterian.

Dr. Cairo highlighted some of the Phase I trials that are either under way or in the planning stages. One Phase I trial will evaluate a radiolabeled antibody called ibritumomab tiuxetan. This antibody is directed against a protein found on lymphoma cells and will be studied in pediatric patients with non-Hodgkin's lymphoma, Hodgkin's lymphoma, and HIV-associated lymphomas.

Another Phase I trial will evaluate a fusion protein called HU 14GD2-IL-2 in children with refractory neuroblastoma and other GD2-positive tumors. This antibody, directed against a tumor protein, is linked to interleukin 2 (IL-2). The concept of the trial is that the antibody will bind to the tumor cells and then IL-2 will attract lymphocytes to the tumor cells and kill them.



Michael A. Weiner, MD:
"Clinical trials ... offered through the COG consortium will provide ... refractory patients with ... the most cutting-edge approaches."

R115777, a farnesyl transferase inhibitor that affects *ras* oncogene signal transduction, will be studied in patients under age 22 with refractory leukemias.

To find out more about these trials, contact the website at www.chony.org

Dr. Weiner can be reached at mw216@columbia.edu

Dr. Cairo can be reached at mc1310@columbia.edu

Phase 1 Experimental Therapeutics

Other Phase I pediatric trials open to accrual at Morgan Stanley Children's Hospital of NewYork-Presbyterian include the following:

- arsenic trioxide for refractory leukemia or lymphoma
- temozolomide and CCNU for incompletely resected non-brain-stem, high-grade gliomas
- flavopiridol in relapsed or refractory solid tumors in lymphomas
- irinotecan plus vincristine in solid tumors, and PS-341 in refractory solid tumors

COX-2 Inhibitors: Anticancer Properties Explored

Over the past decade, a series of studies have suggested that the enzyme cyclooxygenase (COX) represents a therapeutic target for preventing and treating cancer.

Epidemiological studies showed that use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with a reduction in the incidence of several cancers, including colorectal cancer. The discovery that NSAIDs inhibit COX suggested that prostaglandins, the products of COX activity, contributed to carcinogenesis. There are two isoforms of COX, COX-1 and COX-2. Recently, selective inhibitors of COX-2 were developed and approved for the treatment of arthritis and pain. Importantly, there is growing evidence that selective COX-2 inhibitors may also be useful as anticancer agents.

is induced by oncogenes, growth factors, cytokines, and tumor promoters. It is present in increased amounts in multiple tumor types, including colorectal, bladder, head and neck, cervix, pancreas and skin, as well as in non-small cell lung cancer. COX-2 is also commonly over-expressed in a variety of premalignant conditions, including Barrett's esophagus, colorectal adenomas and oral leukoplakia.

The drug being studied by Dr. Dannenberg is celecoxib, which is currently available in the U.S. for treatment of arthritis. "Here we have a drug that was designed to treat arthritis and pain, made its foray into the cancer field as a prevention drug, and is now being fast-tracked into studies to assess its potential role in cancer therapy," he said. Celecoxib is the only drug approved as



Andrew J. Dannenberg, MD, is evaluating the role of COX-2 inhibitors in preventing and treating cancer.

"Because standard cancer therapies like paclitaxel and radiation induce COX-2 expression, inhibitors of the enzyme may be an effective adjuvant to chemotherapy."

— Andrew J. Dannenberg, MD

Andrew J. Dannenberg, MD, Co-Director of Cancer Prevention at NewYork Weill Cornell Medical Center, is currently studying COX-2 inhibitors for the possible prevention and treatment of cancer. COX-1 is expressed in most tissues and appears to be responsible for producing the prostaglandins that mediate normal functions like maintenance of gastric mucosal blood flow. This is why selective COX-2 inhibitors appear to cause less gastrointestinal toxicity than traditional NSAIDs that inhibit both COX-1 and COX-2. However, COX-2 cannot be detected in most normal tissues, but

adjunctive therapy for a rare condition called familial adenomatous polyposis (FAP), which strongly predisposes patients to colon cancer.

The COX-2 inhibitors have numerous effects on cells, blood vessels and the immune system. Various cancers form more prostaglandins than do the normal tissues from which they arise. COX inhibitors inhibit cell proliferation, induce apoptosis, inhibit angiogenesis, reduce carcinogen activation and stimulate the immune system.

There is extensive evidence suggesting that COX-2 is linked to the development of cancer. For example, knocking

out the COX-2 gene protects against the development of intestinal and skin tumors in experimental animals. In addition, selective inhibitors of COX-2 reduce the formation, growth and metastasis of a variety of tumors in certain animals.

The first human trial to evaluate the anticancer properties of selective inhibitors of COX-2 was conducted in patients with FAP. Treatment with celecoxib for six months caused a significant reduction in the number of colorectal polyps compared to placebo ($P=0.003$). The total polyp burden was significantly reduced in patients receiving celecoxib compared to those receiving placebo.

To date, major emphasis has been placed on evaluating the role of COX-2 inhibitors in preventing cancer. Dr. Dannenberg and other investigators at NewYork-Presbyterian Hospital are on the front line of experimental and clinical research into the role of COX-2 inhibitors for both prevention and therapy of several tumor types. Physicians at NewYork-Presbyterian Hospital are participating in a large, randomized, placebo-controlled trial to determine whether celecoxib can prevent the

see COX-2s for Cancer, page 9

Clinical Trials Target Novel Gynecologic Cancer Therapies

The active gynecologic clinical research program at Columbia University's College of Physicians & Surgeons is currently participating in a number of innovative Southwest Oncology Group (SWOG) clinical trials. Amy Tiersten, MD, Director of the Medical Oncology Breast and Gynecologic Clinical Research Program at Columbia Presbyterian Medical Center, is the national principal investigator (PI) for several of these SWOG studies.

She noted that the medical center's participation in these trials, as well as her role as PI, "gives Columbia Presbyterian Medical Center a prominent spot on the national radar screen of what's happening in gynecologic oncology."

Ovarian Cancer Facts

- estimated 23,300 new cases in the U.S. this year
- estimated 13,900 deaths in the U.S. this year (more than any other cancer of the female reproductive system)
- accounts for 4% of all cancers in women
- second most common gynecologic cancer (after that of the uterine corpus)
- incidence declined at a rate of 1.3% per year between 1992 and 1998
- about 80% of new ovarian cancer patients survive 1 year after diagnosis, with 52% surviving (all stages) after 5 years

Source: "Cancer Facts & Figures 2002."
American Cancer Society

"Participation in these trials gives Columbia Presbyterian Medical Center a prominent spot on the national radar screen of what's happening in gynecologic oncology."
— Amy Tiersten, MD

Dr. Tiersten discussed several of the studies. For instance, a Phase II study is evaluating both a new route of administration and some newer drugs as front-line therapy for optimally debulked ovarian cancer. In this study, patients receive intraperitoneal chemotherapy with cisplatin, followed by intravenous paclitaxel; they are then given intraperitoneal paclitaxel plus intravenous liposomal doxorubicin.

A second Phase II study is evaluating neoadjuvant chemotherapy for patients with advanced disease who are not surgical candidates. This is a large SWOG study to evaluate neoadjuvant chemotherapy in ovarian cancer. Patients are given neoadjuvant intravenous paclitaxel and carboplatin for three cycles in an aggressive attempt to debulk the tumor. If the tumor is optimally surgically debulked following this neoadjuvant chemotherapy, then intraperitoneal carboplatin, intravenous paclitaxel, and intraperitoneal paclitaxel are administered.

One of the things that is unique about this particular Phase II trial is that only a cytologic diagnosis is required for enrollment. Patients do not have to undergo surgery for open biopsy. Another feature is that it is one of the first SWOG studies to incorporate intraperitoneal carboplatin instead of cisplatin.

Another trial is a Phase III, intergroup, five-arm ovarian cancer study

designed to evaluate various permutations of front-line combination therapy with sequential doublets and triplets that contain gemcitabine, topotecan, and liposomal doxorubicin in combination with a platinum and paclitaxel. Patients will be evaluated for toxicity and efficacy after six months of treatment and at various points thereafter.

Recurrent ovarian cancer poses a treatment challenge. Two Phase II trials at Columbia Presbyterian Medical Center are evaluating single-agent STI-571 and single-agent irinotecan, respectively, in this setting. This is the first study of STI-571 in ovarian cancer.

Dr. Tiersten had earlier conducted a trial looking at the combination of topotecan and paclitaxel in metastatic or recurrent cervical cancer. The study results were of sufficient interest to move the study to SWOG as a Phase II trial that is now open for accrual, she said.

In addition, another Phase II study is currently under way for CCI-779 (a rapamycin analog) in endometrial cancer. *PTEN*, a tumor-suppressor gene, is frequently mutated in endometrial cancer, she explained. CCI-779 is a biological therapy that exerts downstream inhibition of the Akt (i.e., protein kinase B) pathway, restoring normal *PTEN* function.

Dr. Tiersten can be reached at
tiersten@cancercenter.columbia.edu

Antiangiogenics May Hold Promise for Leukemia

Researchers at New York Weill Cornell Medical Center are identifying new ways to target acute myeloid leukemia with antiangiogenic drugs.

Investigators believe these agents may have a greater impact on leukemia than on solid tumors, according to Eric J. Feldman, MD, Director of the Leukemia Program, Division of Hematology and Medical Oncology. “In leukemia there may be more compelling reasons why antiangiogenic therapy or targeting mediators of angiogenesis has value,” he said. This theory is explained, in part, through the differences between the classic and leukemic models of angiogenesis, as well as the roles of the paracrine and autocrine pathways.

Models of Angiogenesis

In the classic model, solid tumors secrete proteins, namely vascular endothelial growth factor (VEGF), which induces endothelial cells to proliferate, migrate and produce blood vessels that support the growth of additional tumors. Endothelial cells also secrete these growth factors, explained Dr. Feldman.

Opportunity?

Some Differences Between Leukemic and Solid Tumors:

- VEGF receptors are not on the surface of solid tumors, but are on leukemic cells
- solid tumors are stimulated through the paracrine pathway, but leukemic growth is fed through paracrine and autocrine processes

In the leukemic model, based on the research of New York Weill Cornell’s Shahin Rafii, MD, VEGF signaling through VEGF receptor-2 (VEGFR-2) causes increased endothelial migration and proliferation, as well as the release of cytokines. VEGF receptors have never been described on the surface of solid tumors, noted Dr. Feldman, “but on the surface of leukemia cells, there are receptors for VEGF, predominantly VEGFR-1 and VEGFR-2.”

of leukemic cells. Because two pathways drive leukemia and one drives solid tumor growth, antiangiogenics may prove more effective in leukemia.

Clinical Studies

Investigators will examine cells from patients treated with antiangiogenics to determine how VEGF receptors are being expressed. They will also inject leukemic cells into mouse-human xenograft models and treat them in

“There may be more compelling reasons why antiangiogenic therapy or targeting mediators of angiogenesis has value in leukemia.”

— Eric J. Feldman, MD

Another difference between leukemic and solid tumors is that both paracrine and autocrine processes feed leukemia growth, while solid tumors are only stimulated through the paracrine pathway.

In the paracrine process, leukemia cells produce VEGF, which then promotes the occurrence of VEGFR-2 on endothelial cells. This, in turn, promotes endothelial growth and new blood vessel formation, as well as the release of cytokines causing leukemic cells to grow.

“In addition, because the leukemic blast cells have receptors for VEGF, we have this autocrine movement where VEGF is released and causes the growth of leukemic cells by interacting with the receptors on these cells,” Dr. Feldman said.

Therefore, interrupting the paracrine and autocrine pathways with antiangiogenic agents may help block the growth

parallel with patients to determine how therapy might be modified. Many of the drugs being investigated are in early stages of development.

A Phase I trial of a small-molecule tyrosine kinase inhibitor called PTK787, which targets VEGFR-2, is being conducted in patients with AML and myelodysplastic syndrome, alone and in combination with chemotherapy. Dr. Feldman’s team has not fully analyzed the data, but he reports that the trial appears to be going well.

C26, a humanized monoclonal antibody that targets VEGFR-2, is about to enter a Phase I trial. “Based on these studies we’ll move forward into Phase II trials in combination with chemotherapy or other agents,” Dr. Feldman said. “We hope to see positive results.”

Dr. Feldman can be reached at ejf2001@med.cornell.edu

New Therapies and Novel Strategies Combat Leukemia

Both centers of NewYork-Presbyterian Hospital are engaged in an intensive effort to develop new targeted therapies for leukemia, to reduce toxicities related to chemotherapy, and to research innovative approaches such as the development of vaccines.

Leukemia Research at Columbia Presbyterian Medical Center

The advent of imatinib mesylate (STI-571; Gleevec) made targeted therapy for chronic myelogenous leukemia (CML) possible. Although this newly approved drug achieves a high response rate in CML, not all patients respond, and some who do suffer relapse. Imatinib mesylate is used for CML and as targeted therapy for other malignancies with

activated tyrosine kinases. Together with colleagues at Columbia Presbyterian Medical Center, Gwen Nichols, MD, Assistant Attending Physician, and Director of the Hematologic Malignancies Program at Columbia University College of Physicians & Surgeons, is performing laboratory research that will ultimately benefit nonresponders or those experiencing a suboptimal response to imatinib mesylate. Stem cells are harvested in the laboratory for cryopreservation. Aliquots of the stem cells are then used to test the ability of imatinib mesylate and other agents to purge leukemia. The same group is also studying less toxic non-chemotherapy agents to determine if any might be synergistic with imatinib mesylate.

Another area of interest is the search for specific, effective therapies for poor-risk patients with acute leukemia (i.e., those who relapse or have myelodysplastic syndrome). For instance, one pilot study is evaluating the combination of gemtuzumab ozogamicin plus mitoxantrone in these high-risk patients.

Although the concern with this regimen is toxicity, no specific hepatotoxicity was observed in the first four patients entered in a dose-escalation trial. The researchers hope to increase the dosing and demonstrate efficacy.

Also unique to the medical center are preliminary studies of immunotherapy (i.e., vaccines) for chronic lymphocytic leukemia (CLL). A number of patients with CLL achieve true remissions on current therapies. The goal of vaccine therapy is to prolong these remissions

by using vaccines made from patients' tumor cells.

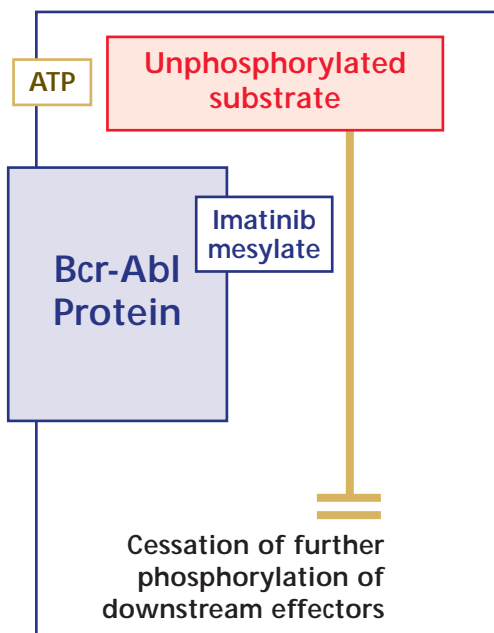
With patients' consent, Dr. Nichols and co-workers are using leftover B-lymphocytes of CLL patients to develop a vaccine. An HLA gene is inserted into

Unique to Columbia Presbyterian are preliminary studies of immunotherapy for chronic lymphocytic leukemia.

the B lymphocytes so that the patient's immune system can recognize the altered B lymphocyte.

"The idea of a vaccine has been circulating for 20 years, but our approach is less cumbersome than previous approaches because it does not rely on patients' DNA. The idea is to collect cells from the peripheral blood before a patient undergoes chemotherapy, for example with fludarabine and rituximab; then, once a patient goes into remission, to utilize a vaccine made from the patients' own lymphocytes to prolong the remission," Dr. Nichols said. If results of current studies are encouraging, then a clinical trial will be mounted. "We are still a ways off from developing a vaccine for clinical use," she said.

Another major area of research at Columbia Presbyterian Medical Center is secondary leukemia in patients who undergo chemotherapy and stem cell transplantation—a rare but devastating complication. In a survey of the first 300 breast cancer patients treated with stem cell transplants, only three developed secondary leukemias, and two of these



The mechanism of action of imatinib mesylate:

Imatinib mesylate occupies the kinase pocket of the Bcr-Abl protein, thus preventing substrate phosphorylation.

had abnormal cells prior to transplantation. The third patient with breast and ovarian cancer developed a secondary leukemia six months after transplant.

Leukemia Research at NewYork Weill Cornell Medical Center

There are three basic approaches to improved treatment of leukemia, explained Eric J. Feldman, MD, Director of the Leukemia Program, Division of Hematology and Medical Oncology, NewYork Weill Cornell Cancer Center. One is using drugs that enhance the activity of chemotherapy, another is employing drugs aimed at novel targets, and a third is developing new cytotoxic agents. He and his colleagues are exploring all three approaches.

As an example of the first approach, NewYork Weill Cornell is participating in a Phase II trial of bryostatin-1 in combination with cytarabine (ara-C), the standard agent for treatment of leukemia. Bryostatin-1 modulates the apoptosis effect of ara-C.

Agents that attack novel targets include PTK787, an oral inhibitor of tyrosine kinase that targets the VEGF-2 receptor. NewYork Weill Cornell is the lead site for a Phase I study of this

agent in acute myeloid leukemia and myelodysplastic syndrome. This campus is also the single site for a Phase I study of the monoclonal antibody IMC 2C6 that also targets the VEGF-2 receptor; this study includes patients with acute myeloid leukemia (AML) and myelodysplastic syndrome.

Other novel targets include those that are thought to be involved in angiogenesis, such as farnesyl transferase. A multicenter Phase II study of the farnesyl transferase inhibitor SCH66366 in a wide range of myeloid malignancies is ongoing.

Dr. Feldman and colleagues have been involved in the development of a novel chemotherapy agent called troxacitabine, which is being studied in AML and chronic lymphocytic leukemia. Troxacitabine is an analog of ara-C but is biologically different from it since it is not susceptible to the same pathways as ara-C.

NewYork Weill Cornell Medical Center was also the lead institution in a pivotal Phase III trial of HUM195, an anti-CD33 antibody. That study included 200 patients with relapsed

Dr. Feldman and colleagues have been involved in the development of a novel chemotherapy agent called troxacitabine, which is being studied in AML and chronic lymphocytic leukemia.

AML from 60 sites. Although HUM195 combined with chemotherapy improved remission compared with chemotherapy alone, the results were not statistically significant, said Dr. Feldman, who reported the results at the recent ASCO meeting in Orlando, Florida. Further study of this drug is under discussion with the sponsor of the trial.

“This drug is not Gleevec,” Dr. Feldman noted. “Gleevec raised the bar too high. We may not see another Gleevec for some time.” Perhaps, but both centers of NewYork-Presbyterian Hospital are looking.

Dr. Nichols can be reached at
nichols@cuccfa.ccc.columbia.edu

Dr. Feldman can be reached at
ejf2001@med.cornell.edu

COX-2s for Cancer

continued from page 5

recurrence of precancerous adenomatous polyps of the colon. The use of COX-2 inhibitors for other tumor types is also being studied at NewYork-Presbyterian Hospital. Investigators in the Department of Dermatology are conducting a study in collaboration with the University of California, San Francisco to evaluate celecoxib for preventing the development of basal cell carcinomas in patients with the nevoid basal cell carcinoma syndrome.

Investigators are participating in a multicenter clinical trial of the COX-2 inhibitor celecoxib in patients with Barrett's esophagus, a premalignant

condition of the esophagus, which increases the risk of adenocarcinoma of the esophagus by 30- to 125-fold. Another multicenter trial uses a COX-2 inhibitor in the treatment of premalignant oral lesions.

There is growing interest in determining whether selective COX-2 inhibitors are also useful for treating cancer. Because standard cancer therapies like paclitaxel and radiation induce COX-2 expression, inhibitors of the enzyme may be an effective adjuvant to chemotherapy regardless of the level of the enzyme prior to treatment. In fact, the role of celecoxib as an adjunct to

preoperative chemotherapy was just evaluated in patients with resectable non-small cell lung cancer. According to Dr. Dannenberg, “The results of this Phase II trial, led by Nasser Altorki, MD, in the Department of Cardiothoracic Surgery, were sufficiently encouraging to justify carrying out a much larger trial.” In addition to lung cancer, the potential role of COX-2 inhibitors as anticancer agents is being assessed in a variety of other tumor types, including colorectal cancer.

Dr. Dannenberg can be reached at
ajdannenberg@med.cornell.edu

Whipple

continued from page 1

pancreatectomy procedures performed each year at the Columbia Presbyterian and New York Weill Cornell Medical Centers of New York-Presbyterian Hospital—one of the largest such experiences in the world. About half of these are done at Columbia Presbyterian where Dr. Allen O. Whipple first developed the procedure and where the mortality rate was recently calculated at only 0.5% per year. By contrast, current data from the Centers for Medicare and Medicaid Services (formerly HCFA) place the national average at more than 5%.

“There is probably no single thing we do differently that would explain our low complication rate. It comes from experience that ranges from preoperative planning to handling problems, such as unexpected bleeding, when they occur,” said John A. Chabot, MD, Medical Director of Operating Rooms, Columbia Presbyterian Medical Center. “The national mortality rate is high because many Whipples are done at hospitals where there is very limited experience.”

‘In about two-thirds of the cases in which we pretreat the tumor, we are proceeding to surgery and getting the tumors out safely.’

—John A. Chabot, MD

John M. Daly, MD, Chairman of the Department of Surgery, New York Weill Cornell, agrees. With more than 50 procedures per year, a highly developed protocol is in place that facilitates effec-

tive staging and surgical planning, permitting the least invasive procedure for the greatest likelihood of an adequate resection. For example, the physicians at New York Weill Cornell employ a laparoscopic approach to resect pre-malignant tumors in the tail of the pancreas.

“For the right candidate, the laparoscopic procedure can reduce the hospital stay from one week to two days, and the morbidity is quite low,” Dr. Daly observed. These candidates are often identified intraoperatively, because at both centers the operation begins laparoscopically. The open procedure is only initiated when laparoscopy confirms that the patient is a candidate for resection, a situation not always accurately predicted with imaging alone.

“About 5% to 10% of the time, the laparoscopic exploration reveals that the patient is not suitable for a

Whipple and we do not proceed,” Dr. Chabot said. “This circumvents the need to abandon an open procedure with its greater morbidity.”

Candidates who might benefit from the Whipple procedures are increasing at both centers, where investigators are looking into protocols that will identify

patients earlier and get them to surgery while the tumor is still resectable. Both centers are also developing operations appropriate for previously inoperable cases. The New York Weill Cornell team

The simple explanation for the very low rate of mortality is the experience drawn from more than 100 combined pancreatectomy procedures being performed each year at the two centers—one of the largest such experiences in the world.

has been researching advanced techniques of cytologic lavage to increase diagnostic sensitivity to the presence of malignant cells. The Columbia Presbyterian team has been using aggressive chemotherapy and radiation to shrink tumors that would otherwise be unresectable.

“In about two-thirds of the cases in which we pretreat the tumor, we are proceeding to surgery and getting the tumors out safely. We have about a year and a half of experience with this approach, so we do not yet have data on whether we are improving survival, but there has been no excessive morbidity or mortality,” Dr. Chabot reported.

Credit for the very low rates of complications from the Whipple procedure and the encouraging cure rates, now approaching 20%, were attributed to the multidisciplinary teams at the New York-Presbyterian Hospital centers.

“It is no one thing. It is patient selection. It is experience. It is perioperative management. Everything contributes,” Dr. Daly said. “It’s all reflected in the results, and we are seeing low rates of complications and the potential for increasing rates of cure.”

Dr. Daly can be reached at jmdaly@med.cornell.edu

Dr. Chabot can be reached at jac4@columbia.edu

NMDP Centers

continued from page 1

- Evaluation of a protocol for purging lymphoma cells in patients undergoing autologous transplantation. During cell collection, nickel particles are impregnated with monoclonal antibodies (Mabs) that adhere to the lymphoma cells; an electromagnet then attracts the contaminated lymphoma cells, allowing the noncontaminated cells to be decanted.
- A dendritic cell vaccine has been developed, and preliminary results from the first 12 patients are encouraging. The vaccine is made from a myeloma protein isolated from the patient's blood. Once the patient has been treated for myeloma, the vaccine is used to treat minimal residual disease by stimulating the immune system.
- Nonmyeloablative transplantation is being studied in patients over the age of 60. This regimen includes doses of both chemotherapy with fludarabine and immunotherapy with alemtuzumab that are lower than are normally employed in the treatment setting. "The novel aspect of this study is the use of both chemotherapy and immunotherapy. We feel alemtuzumab

BMT Programs

Columbia Presbyterian Medical Center offers both an adult and pediatric program where allogeneic transplants are performed; NewYork Weill Cornell Medical Center has an adult program for both related and unrelated allogeneic transplants.

The oncology programs at Children's Hospital of NewYork-Presbyterian provide the highest quality care through the Herbert Irving Child & Adolescent Oncology Center at the Morgan Stanley Children's Hospital and the Division of Pediatric Hematology/Oncology at NewYork Weill Cornell Medical Center.

mab will be useful in allowing better engraftment," Dr. Schuster said.

- Other studies at NewYork Weill Cornell include the investigation of a new radiolabeled antibody (yttrium-labeled anti-CD22) in patients with non-Hodgkin's lymphoma, and a study using a monoclonal antibody called HUM195 as part of a conditioning regimen for patients with acute myelogenous leukemia.

Columbia Presbyterian Medical Center Programs

Charles Hesdorffer, MD, Director of the Adult Bone Marrow and Stem Cell Transplantation Program, described some recent important advances.

Dr. Hesdorffer noted that one major advance has been the realization that it is not necessary to have six out of six HLA matches for patients undergoing allogeneic transplantation; haploid identical transplants—that is, three or four out of six matches—can be used for allogeneic transplantation with a donor who is a first-degree relative. A second advance is based on the finding that myeloablative conditioning using high doses of chemotherapy and radiotherapy is not needed and that nonmyeloablative regimens using lower doses of chemotherapy are both feasible and effective. The evidence for use of mismatched marrow came from work by Yair Reisner, MD, at the Weizmann Institute of Science in Rehovot, Israel, Dr. Hesdorffer explained.

Dr. Reisner found that one might bypass rejection by giving a large number of stem cells, which results in less graft-versus-host disease (GVHD).

Working with a group of investigators from Perugia, Italy, 150 patients with hematologic malignancies were treated with large numbers of haploid identical stem cells, and all patients were engrafted. GVHD complications were surprisingly low in this group of patients.

Now, Columbia Presbyterian Medical Center is one of four centers in the U.S. trying to emulate these findings

using large numbers of stem cells. About 100 patients with hematologic malignancies have been entered in a four-center study, composed of Columbia Presbyterian, M.D. Anderson Cancer Center, City of Hope, and Stanford University.

If the encouraging results in the Perugia study are borne out, it will be possible to find a donor for most people without having to resort to a registry. This would expand the recipient pool by expanding the donor pool.

The opposite approach is to expand the recipient pool by realizing that dose intensity is not as important as graft-versus-tumor effect, he continued. This has led to a nonmyeloablative approach to allogeneic transplantation at Columbia Presbyterian Medical Center and other centers.

"Instead of whopping doses of chemotherapy, we give smaller doses. This reduces the side effects of chemotherapy. Then we give larger doses of stem cells and hope that with time, the stem cells will take over the patient's marrow," Dr. Hesdorffer commented.

The current focus of the program is to stimulate the graft-versus-tumor effect rather than reduce GVHD.

"This is all based on knowing how to identify and stimulate the right cells. Our program has been studying ways to stimulate the graft-versus-tumor effect by relying on cellular immunotherapy rather than cytotoxic chemotherapy," Dr. Hesdorffer concluded.

Pediatric Programs at Morgan Stanley Children's Hospital of NewYork-Presbyterian

Morgan Stanley Children's Hospital of NewYork-Presbyterian is a leader in performing reduced-intensity (nonmyeloablative) allogeneic transplantation in children with malignancies and genetic diseases, and is also a leader in performing nonmyeloablative transplants using unrelated cord blood as the donor source, explained Mitchell S. Cairo, MD, Director, Pediatric BMT

NMDP Centers

continued from page 11

Program, and Director, Pediatric Cancer Research, Morgan Stanley Children's Hospital of NewYork-Presbyterian. The program is "probably one of the top five Unrelated Cord Blood Transplant Centers in the United States," Dr. Cairo said.

A current approved protocol for children with lymphoma and neuroblastoma employs high-dose chemotherapy and autologous stem cell transplant, followed by nonmyeloablative or reduced-intensity chemotherapy with allogeneic stem cell transplant.

"The concept is to give high-dose chemotherapy and rescue the patient with his or her own cells, reducing the cancer burden by following that with low-dose chemotherapy and

inducing a graft-versus-tumor effect," Dr. Cairo noted.

An innovative study to reduce GVHD in children employs a combination of tacrolimus and mycophenolate mofetil. An advantage of using this approach to prevent GVHD in children is that it avoids the use of steroids and prednisone. Thus far, the study has had encouraging results.

Investigators are also performing basic research in pediatric oncology in a variety of areas, including the molecular basis of childhood lymphomas and leukemias, whose efforts are aimed at identifying unique genes as targets of post-transplant immunotherapy. Another area of study attempts to understand how tolerance develops

between the donor cells and the patient's cells in the hope that this might lead to the prevention of rejection.

In addition, dendritic cells are being studied for their potential to coordinate immune cells that kill tumors. Ways of training donor cells to become killer cells once given to the recipient are also under study.

Dr. Cairo can be reached at
mc1310@columbia.edu

Dr. Hesdorffer can be reached at
hesdorffer@cancercenter.ccc.columbia.edu

Dr. Schuster can be reached at
mwschust@mail.med.cornell.edu

SERVICE LINE ADMINISTRATOR: Susan Silverman, 627 West 165th Street, New York, NY 10032, 212.305.1340 E-mail: sus9005@nyp.org

Volume 1, Number 1

NewYork-Presbyterian Hospital
525 East 68th Street
New York, NY 10021

Nonprofit Org.
U.S. Postage Paid
Permit No. 7925
New York, NY

**Important news from
the Cancer Centers of
NewYork-Presbyterian
Hospital, at the fore-
front of cancer preven-
tion and screening,
diagnosis, treatment,
basic science and
clinical research.**