

NEW YORK-PRESBYTERIAN Oncology

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Advancing Outpatient Laparoscopic Surgery in Colon Cancer

Minimally invasive laparoscopic colorectal surgery is one of the fastest-growing procedures worldwide. NewYork-Presbyterian Hospital is one of the major centers contributing to this growth.

Researchers at NewYork-Presbyterian Hospital and Columbia University College of Physicians & Surgeons—led by Richard L. Whelan, MD—and NewYork-Presbyterian Hospital and Weill Medical College of Cornell University—led by Jeffrey Milsom, MD—are investigating several lines of study, including the feasibility of outpatient laparoscopic colorectal surgery on patients with colorectal cancer, as well as hand-assisted laparoscopic surgery. They are also investigating the immunologic and oncologic effects of conducting surgery via traditional large-incision methods versus minimally invasive laparoscopic, page 5

Coordinating Research Efforts In the Treatment of Melanoma

Major initiatives are under way to bring together experts on skin cancer from NewYork-Presbyterian Hospital and its 2 affiliated medical schools—Columbia University College of Physicians & Surgeons and Weill Medical College of Cornell University—to strengthen existing research programs and implement the latest protocols in the treatment of melanoma, one of the deadliest of skin cancers.

“Approximately 8,000

Americans die from melanoma each year,” said David R. Bickers, MD. “For years, research in skin diseases didn’t attain the kind of high priority from the National Institutes of Health, for example, as conditions like heart disease. Yet the skin is the body’s largest organ and one of our major environmental interfaces.” Federal agencies such as the National Institute for Occupational Safety and Health have reported that skin diseases are one of the major causes of time lost from work, due to various chemical exposures.

At NewYork-Presbyterian/Columbia, one of the most important efforts to raise the profile of melanoma research has been the establishment of the Multi-disciplinary Melanoma Center. Opened within the Hospital’s Herbert Irving

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A typical melanoma: Major initiatives are under way at NewYork-Presbyterian Hospital to strengthen existing research programs and implement the latest protocols in the treatment of melanoma, one of the deadliest of skin cancers.

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Monahan Center Incorporates Gastrointestinal Cancer Research and Treatment

The Jay Monahan Center for Gastrointestinal Health, a collaboration of NewYork-Presbyterian Hospital and Weill Medical College of Cornell University, offers a world-class mix of patient treatment, education, and clinical research services.

For patients, the Center, which opens in March, provides seamless, multidisciplinary care through a core team made

up of 2 gastroenterologists, a surgeon, 2 oncologists, and a nurse coordinator, who helps patients diagnosed with GI cancer navigate the medical care system. The core team is available to meet with patients and communicate among specialists for all aspects of a patient's care. Patients will have access to genetic counselors, social workers, psychologists, nutritionists, and home care services.

"It used to be a luxury to have a geneticist sit down and review things with patients," said Mark Pochapin, MD. "But that is something that we really think is important, as is nutrition counseling. Clearly, this place is going to be unique. The people who were chosen to work here are very caring, responsible, and compassionate. It's not going to be a place where patients just get shuttled in and out of rooms."

The Monahan Center is named in honor of Jay Monahan—the late husband of NBC "Today Show" co-anchor Katie Couric. An active and health-conscious man in the prime of his life, Monahan was diagnosed unexpectedly with advanced colon cancer at the age of 41. In the months following his diagnosis, he and his family were traumatized not only by his illness, but also by the exhausting effort needed to collect information and identify treatment options. Monahan battled the disease for several months. He died in 1998.

In 2000, Couric brought attention to the need for further research in the area of gastrointestinal cancers by putting together a five-part series of broadcasts entitled "Confronting Colon Cancer," during which she underwent a colonoscopy live, on national television. Dr. Pochapin, who was Monahan's gastroenterologist, took part in the series. A year later, a follow-up series won the prestigious Peabody Award for broadcast journalism.

"The most amazing part was that after that segment aired, investigators looked at the rates of colonoscopy, and they had jumped by almost 20%," said Dr. Pochapin. "I realized that the 5 minutes I spent on the 'Today Show' probably saved more lives than I may have been able to do in a career as a physician."

"Clearly, [the Monahan Center] is going to be unique. The people who were chosen to work here are very caring, responsible, and compassionate. It's not going to be a place where patients just get shuttled in and out of rooms."

—Mark Pochapin, MD



At the Monahan Center, GI cancer patients will have access to genetic counselors, social workers, psychologists, nutritionists, and home care services.

This phenomenon, dubbed the “Couric Effect” by researchers at the University of Michigan Health System and the University of Iowa, was the subject of an article in *Archives of Internal Medicine* last year [2003;163:1601-1605].

After Monahan’s untimely death, his family pledged to find a better way for future patients—and for those in whom this devastating disease might be prevented. It was through their courage and vision—and the generous support of the Entertainment Industry Foundation’s National Colorectal Cancer Research Alliance—that the Jay Monahan Center for Gastrointestinal Health was established. Dr. Pochapin said he had always been intrigued by the idea of creating a multidisciplinary GI center.

“We had a lot of discussions with Katie, and she loved the idea,” he said. Through her association with the National Colorectal Cancer Research Alliance, Couric was instrumental in helping to raise the funding needed to establish the center.

According to Dr. Pochapin, physicians at the Center will have the resources to evaluate and offer new therapeutic approaches to prevention and treatment of gastrointestinal cancers, from the latest diagnostic equipment to alternative and holistic options.

“We want people to look to the Monahan Center as a source of information about gastrointestinal cancer, not only what to do to treat it but, equally as important, how to prevent it,” said Dr. Pochapin. “In fact, we have a dedicated education specialist in charge of education and outreach [on staff].”

The Center will also provide a universal referral service for information on clinical outcomes, research protocols, prevention, and treatment. Research will focus on the most promising clinical trials, ensuring the latest and most effective patient care options.

“We’ll have many protocols at the Center,” Dr. Pochapin said, “but if we don’t have something [that] a patient is interested [in], we’ll find out where that is for them. I want people to point to the Monahan Center and say, ‘This is the way medicine should be practiced.’”

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NewYork-Presbyterian Oncology is a publication of the Cancer Centers of NewYork-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 NewYork-Presbyterian Hospital/Columbia University Medical Center and the Weill Cornell Cancer Center at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, which are respectively comprised of physicians from the Columbia University College of Physicians & Surgeons and the Weill Medical College of Cornell University.

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New Chemo Regimen May Improve Response Rate in Advanced Pancreatic Cancer

Researchers at New York-Presbyterian Hospital and Columbia University College of Physicians & Surgeons are experimenting with a new and potentially synergistic combination chemotherapy regimen for advanced pancreatic cancer. The regimen, known as GTX (Gemzar-Taxotere-Xeloda), was designed to exploit biochemical synergies that Robert L. Fine, MD, and his team of investigators had observed in the laboratory.

In a recent review of GTX, responses were noted in more than half of all patients who received it. "We are not curing patients, but we are certainly improving responses and quality of life," said Dr. Fine. "The ultimate goal is helping patients live a lot longer with this disease."

New investigations are clearly warranted in locally advanced pancreatic cancer, which has "an exceedingly high mortality rate," noted Shermian A. Woodhouse, MD, MPH. Dr. Woodhouse is working with Dr. Fine and Ronald D. Ennis, MD, on research in this area.

"We are not curing patients, but we are certainly improving responses and quality of life. The ultimate goal is helping patients live a lot longer with this disease."

—Robert L. Fine, MD

"Traditional radiation techniques are limited by the sensitivity of the surrounding normal tissues to radiation, which significantly limits the dose of radiation that can be safely given using external beam," said Dr. Woodhouse. "The response rate in the published reports of Gemzar are certainly promising, as the results seem to be better than with 5-FU, which is the traditional or standard treatment."

In the laboratory, the antitumor activity of the GTX combination seems to be synergistic; apoptosis can be induced without high concentrations of drugs. The regimen carried forward to clinical investigations is a 2-week course (oral Xeloda given on days 1

through 14, along with Gemzar and Taxotere on days 4 and 11) repeated every 21 days. Investigators have reported on 44 patients (median age, 64 years) who have all received GTX. Of that group, 32 patients had pancreatic cancer with liver metastases. The other 12 patients had surgically inoperable disease without liver metastases.

Response was evaluated after 3 cycles. For the 32 metastatic patients, partial tumor response (tumor reduction of at least 50%) occurred in 15 (47%), while another 10 patients (31%) had stable disease. By cycle 8, 3 patients were completely free of all metastatic disease. For the 12 inoperable patients, treatment included the 3 cycles of GTX, followed by radiation, then a Whipple procedure. Eight patients had a complete response (successful Whipple and normal serum levels of tumor marker CA19-9), while 3 patients had a partial response (microscopic positive margins). The regimen seems to be well tolerated. Major toxicities included grade 3 diarrhea, leukopenia, asthenia, and hand-foot syndrome in 20% to 25% of patients. There were no neutropenic fevers or deaths.

"Some of these patients with metastatic disease are living as long as 3

GTX Regimen in Pancreatic Cancer Metastatic to Liver: Response at 3 Cycles

Patients (n)	Partial Response (PR)	Stable Disease (SD) or Minor Response	No Response	Clinical Benefit (PR+SD)
All (32)	15* (47%)	10 (31%)	7 (22%)	25 (78%)
Subset of patients who previously failed:				
CPT-11/ Gemzar (4)	2 (50%)	2 [†] (50%)	0	4 (100%)
Gemzar alone (6)	2 (33%)	2 (33%)	2 (33%)	4 (66%)

*Of these 15 patients, 3 had a clinically complete response of all metastatic disease by cycle 8.

[†]Includes 1 minor response (tumor shrinkage of less than 50%).

years,” Dr. Fine said.

Dr. Fine cautions that while results to date are promising, a carefully designed Phase III, randomized trial must be undertaken to confirm the apparent benefits of GTX. Dr. Ennis, who has looked at combining the regimen with radiation, agrees.

“The addition of Gemzar a few years ago was a significant advance in the treatment of advanced pancreatic cancer, but now, this new combination appears significantly better than what we had been using,” said Dr. Ennis. “We are able to shrink down tumors in combination with radiation, making

surgery possible much more often than in the past. Since surgery is the only cure, shrinking the tumors to make them operable is crucial, so GTX is very effective in allowing us to try to cure more people. We are also able to prolong the lives of people who cannot be cured.”

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Laparoscopic

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sive laparoscopic techniques.

At NewYork-Presbyterian/Weill Cornell, Dr. Milsom and colleagues are evaluating whether minimally invasive cancer surgery can be effective on an outpatient basis. They are performing major laparoscopic resections of the small and large intestines and determining whether patients have recovered sufficiently for discharge within 24 hours. The investigators plan to study how to reduce patient stress from anesthesia as well as the efficacy of nonnarcotic pain medication in this setting.

Laparoscopic procedures sometimes take 30 to 60 minutes longer than open surgery, according to Dr. Milsom. However, laparoscopy results in better outcomes, fewer complications, and faster recovery than open surgery.

Dr. Milsom is also evaluating a hand-access device called GelPort to help optimize success in hand-assisted laparoscopic surgery. “GelPort allows us to make a small incision in the pubic hair line area, similar to what women have for C-section,” he explained. Physicians are then able to perform complex procedures using laparoscopic tools. Patients

recover quickly and scars are not as prominent as with an open procedure.

Dr. Milsom and colleagues conducted a retrospective study (*Surg Endosc* 2003 Sep 10) of 33 hand-assisted laparoscopic colorectal procedures including total colectomy (n=16) and low anterior resection (n=10). In this study, 3 (9.1%) of 33 hand-assisted laparoscopic surgical procedures were converted to open surgery, and 4 (13.3%) required minimal enlargement of incisions to facilitate extracorporeal procedures. The operative time was 263±85 minutes, and the blood loss was 282±148 mL. There were no device malfunctions. Three major complications (9.1%) and 7 minor wound infections (21%) were noted postoperatively. The mean hospital stay was 7.9±3.8 days. According to Dr. Milsom, the study showed that, when performed with GelPort, hand-assisted laparoscopic surgery is safely and reliably applicable for various colorectal procedures.

At NewYork-Presbyterian/Columbia, a team led by Dr. Whelan is evaluating the oncologic, immunologic, and physiologic factors related to laparoscopic surgery, and has published more than 65 articles on the topic. Dr. Whelan and his colleagues are currently researching why colorectal cancer patients who undergo laparoscopic surgery have a longer dis-

ease-free survival than those who undergo an open procedure. Research suggests that subjects with colorectal cancer who undergo laparoscopy have a lower risk of tumor recurrence than those who have open surgery, according to Dr. Whelan (*Lancet* 2002;359:224-229).

“We’re looking at how avoiding the incision of open surgery impacts cancer recurrence,” he said.

Dr. Whelan and colleagues demonstrated (*Surgery* 2002;32:186-192) that plasma from colorectal cancer patients who had undergone major open surgery was depleted of a tumor suppressor protein, known as insulin-like growth factor binding protein 3 (IGFBP-3). In a study of 84 patients, 45 underwent open operations and 39 underwent laparoscopic procedures. The preoperative IGFBP-3 levels were similar in both groups. However, unlike the open or large-incision colon operations, the laparoscopic operations did not appreciably lower the level of IGFBP-3. The researchers found that the open patient’s plasma taken 1 day after the operation stimulated cultured tumor cells to grow to a significantly greater extent than did their preoperative plasma. The degree of stimulation of tumor growth correlated directly with the length of the incision, according to

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Laparoscopic

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Dr. Whelan. His team has determined the duration of the detrimental effects due to lack of IGFBP-3 after open surgery is about 3 to 4 days.

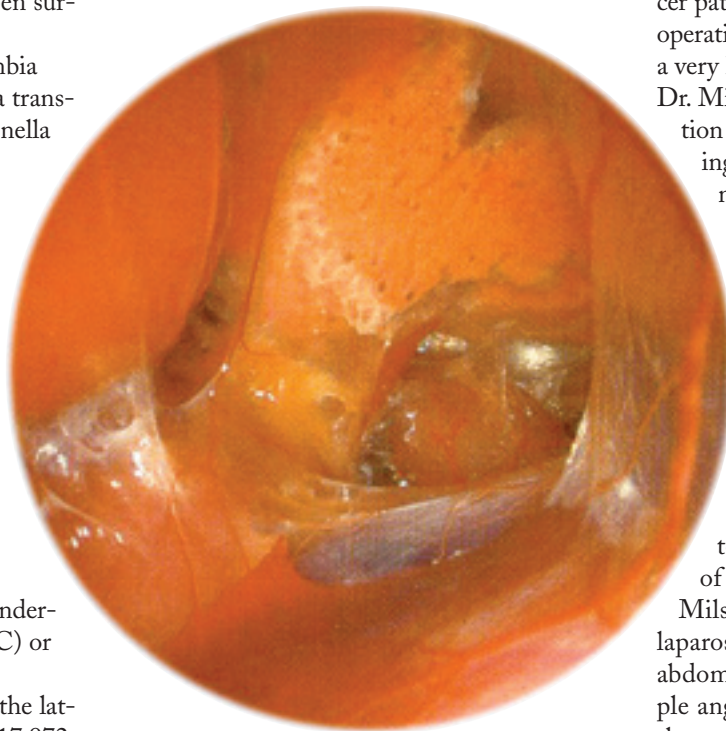
NewYork-Presbyterian/Columbia researchers have also developed a transfected modified version of salmonella inserted with IGFBP-3. When injected into animal models and coupled with radiation treatment, the salmonella reduces tumor size within 2 weeks. These same investigators are planning to study the agent plus radiation in humans with colorectal cancer in the hope of avoiding surgery.

Dr. Whelan and his team have also assessed cell-mediated immune function via serial delayed-type hypersensitivity (DTH) skin testing in patients undergoing laparoscopic colectomy (LC) or open colectomy (OC) and found immunosuppression occurs with the latter procedure (*Surg Endosc* 2003;17:972-978). Altogether, 35 subjects underwent either LC (n=18) or OC (n=17) in this prospective, nonrandomized study.

When the results of the day-of-surgery DTHs were compared between the 2 groups, the LC group's median percentage change from baseline was significantly less than that observed in the OC group (LC, -21%; OC 88%; $P < 0.004$). "This study helps to confirm that there is less immunosuppression after laparoscopy," said Dr. Whelan.

In another study (*Surg Endosc* 2003; May:754-757), Dr. Whelan and his research team concluded that the percentage of CD3+CD31+ cells decreases following open surgery but not laparoscopic surgery and may be related to incision length. This may compromise T-cell function in the peripheral tissues in the postoperative period. The study eval-

uated the peripheral blood of 27 open surgery and 24 laparoscopic surgery colon cancer patients preoperatively and on postoperative days 1 and 3. CD31+ T cells were assessed with flow cytometry using monoclonal antibodies.



A cancerous colon. Researchers are investigating outpatient laparoscopic colorectal surgery in patients with colorectal cancer.

In the open surgery group, the percentage of CD3+CD31+ cells was significantly lower in both postsurgery samples compared to the preoperative results. However, laparoscopic surgery did not result in a significant change in the percentage of these T cells. A significant correlation was found between the decrease in the percentage of CD3+CD31+ cells and the length of incision in open surgery patients.

Dr. Whelan and his team are also conducting a randomized clinical trial of granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with colorectal cancer given before and after surgery. "So far, it looks promising," said

Dr. Whelan, adding that NewYork-Presbyterian Hospital is the only place in the country offering such therapy to colorectal cancer patients.

Technologies that may complement laparoscopic procedures in colorectal cancer patients include advancements in the operating room. "We're trying to develop a very high-tech operating room," said Dr. Milsom. This includes the coordination of new tools, new image processing, and operating rooms that communicate with one another.

Such technology allows surgeons to take control of the operating room environment, he said. For example, voice-control technology can help the physician adjust operating room lighting and instrument controls and manage other tools used in an operation.

Physicians are also moving toward the photodocumentation of surgery, according to Dr. Milsom. Small digital cameras laparoscopically placed inside the abdomen can visualize organs at multiple angles and record images during the various stages of an operation.

Among the drawbacks of these innovations are the learning curve and the costs associated with these new technologies, noted Dr. Milsom. "We have not even scratched the surface of the technologies that can be brought into the operating room. This is an exciting time for surgery."

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Melanoma

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Comprehensive Dermatology and Skin Cancer Center (part of the Skin Disease Research Center) in collaboration with the Department of Surgery and the Division of Medical Oncology in July 2002, the Center will move to a dedicated space later this year.

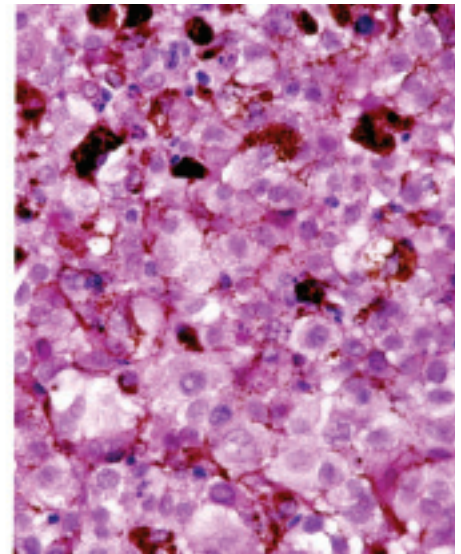
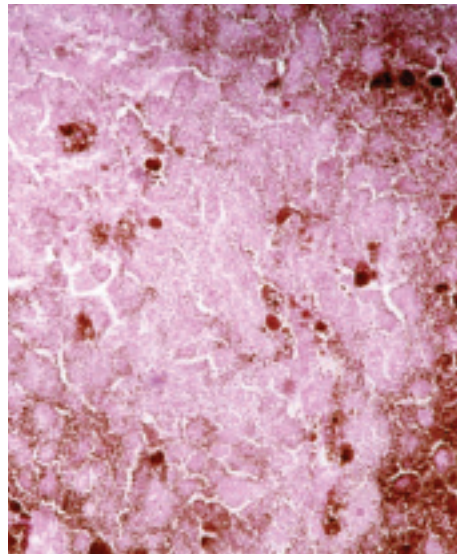
“Melanoma is truly a multiorgan system disease,” said Desiree Ratner, MD. “Although it originates in the skin, it has significant metastatic potential.” Thanks to the Multidisciplinary Melanoma Center, Dr. Ratner added, “if, after excisional biopsy of the lesion, we determine that a patient needs a sentinel lymph node biopsy in addition to wide excision,” the Hospital can refer that patient to an expert on the subject immediately.

The Center’s leadership has formed a team of experts to meet weekly and develop clinical plans for the management of new or difficult patients. The team includes experts in the fields of dermatology; medical, surgical, and radiation oncology; pathology; and radiology.

“We offer the full range of services for melanoma, including plastic surgery [for reconstruction] and immuno- and chemotherapy,” noted Howard Kaufman, MD. “Patients come from all over for second opinions or even treatments that aren’t available elsewhere,” including local hospitals.

At NewYork-Presbyterian/Weill Cornell, researchers have also focused on a multidisciplinary approach in the area of melanoma. Researchers on both campuses are exploring ways to eventually create a joint program linking their efforts in melanoma treatment.

The question of who gets skin cancers (including melanoma) is a critical research area at NewYork-Presbyterian/Weill Cornell. According to Richard D. Granstein, MD, if “you take a group of patients who are more easily affected by ultraviolet [UV] radiation, the research indicates the possibility that UV easily suppresses their ability to become immunized.” Dr. Granstein is also involved in another project exploring tumor antigens.



Pretreatment biopsy of a patient with metastatic melanoma to multiple subcutaneous sites (left). Following treatment with tumor-infiltrating lymphocytes (TILs) transduced with the gene for tumor necrosis factor (TNF) plus interleukin-2, a biopsy of another lesion showed massive coagulative necrosis of the tumor with no viable tumor seen (right).

“Our laboratories have demonstrated that Langerhans’ cells present tumor antigens for activation of the immune system,” he said. “There’s a lot of evidence that the immune system is involved in the control of skin cancer,” including squamous cell carcinomas but also basal cell carcinoma and melanomas.

In a similar vein, at the Multidisciplinary Melanoma Center, researchers are taking “total periodic body photos” of patients using MoleMap photography. They are focusing primarily on patients with a large number of moles who might develop melanoma (ie, those with a family history).

“The body photos are stored on a CD-ROM to keep as a baseline record,” noted Dr. Ratner. Every time the patient returns to the Center for a checkup, she added, doctors can compare their skin “to the baseline photo to see if a mole has changed or if there are new moles.”

Coordinating research efforts among the various centers and departments allows NewYork-Presbyterian researchers to compare the efficacies of a number of treatment options.

Other procedures are being studied for other types of skin cancer. The Dermatologic Section at NewYork-Presbyterian/Weill Cornell, for instance, is

currently exploring the efficacy of Mohs’ micrographic surgery. The procedure allows for the removal of aggressive skin cancers and cancers that occur in certain anatomic sites—including the lips, face, and nose—that have a higher risk of recurrence.

“Mohs’ surgery offers the highest possible cure rates for selected cancers and allows me to approach reconstruction knowing that tumor-free margins have been obtained by the most sensitive means available,” said John A. Carucci, MD, PhD.

At NewYork-Presbyterian/Columbia’s Multidisciplinary Melanoma Center, meanwhile, researchers are studying the use of high-dose interleukin-2 for patients with metastatic melanoma. According to Dr. Kaufman, this relatively new treatment “works on about 20% of patients, extending their lives [on average] 4 years.” Retreatment after that can extend some patient’s lives even further. “We have 2 patients who appear to have been cured,” he continued. Researchers are working with Steven Isaacson, MD, a radiation oncologist at NewYork-Presbyterian/Columbia, on a study testing the use of interleukin-2 as a follow-up to gamma knife surgery for

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Lung Cancer: Investigational Treatment Approaches Yield Promising Results

Investigators at NewYork-Presbyterian Hospital and Weill Medical College of Cornell University are pursuing multiple lines of research that may lead to significant advances in the treatment of lung cancer.

The researchers have shown for the first time that COX-2 inhibitors might boost the effectiveness of chemotherapy. They have also demonstrated that targeted immunotherapy may be promising for the treatment of lung cancer.

received 400 mg of the COX-2 inhibitor celecoxib twice daily along with 2 cycles of preoperative paclitaxel-carboplatin. End points of the Phase II trial were toxicity, response, and levels of prostaglandin E₂ (PGE₂), a molecule associated with tumor growth.

All 29 patients completed chemotherapy, and 26 completed preoperative celecoxib. The overall clinical response rate was 65%, comprising 48% partial response and 17% complete response,

multicenter Phase II trial, Dr. Altorki and colleagues will evaluate tumor response rate and survival in non-small-cell lung cancer patients who receive chemotherapy and celecoxib versus those who receive chemotherapy alone. NewYork-Presbyterian/Weill Cornell researchers have also completed preliminary trials of antigen-specific immunotherapy in patients with non-small-cell lung cancer.

In particular, there is interest in targeting the MAGE-3 antigen, which is expressed in an estimated 40% of lung cancer patients' tumors, and NY-ESO-1, which may be expressed in 20% of those with lung cancer.

In preliminary trials, results of which are soon to be published, researchers demonstrated that vaccinated individuals mounted an immune response, measured both by antibody levels and by activated T cells. In the near future, there will be 2 follow-up trials evaluating 2 different vaccines. The goal is to see if the immune response successfully generated in the preliminary trials can translate into an anticancer effect.

"If, in fact, immunotherapy works for cancer treatment, then there is a whole new avenue open where we could conceivably control the balance between the host and the cancer," Dr. Altorki said. "Just as people with hypertension live a long life if they control their blood pressure, people with cancer could live a long time, not necessarily eradicating the cancer, but coexisting with it."

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"Our goal is to develop more tumor-specific therapies that would have minimal toxicity and have a greater effect on the tumor than traditional chemotherapy or radiation. That achievement relies on our understanding of the molecular mechanisms involved in controlling tumor growth."

—Nasser K. Altorki, MD

"Our goal is to develop more tumor-specific therapies that would have minimal toxicity and have a greater effect on the tumor than traditional chemotherapy or radiation," said Nasser K. Altorki, MD. "That achievement relies on our understanding of the molecular mechanisms involved in controlling tumor growth."

Last year, the *Journal of Clinical Oncology* published the first study showing that a COX-2 inhibitor may enhance the effectiveness of standard chemotherapy (2003;21:2645-2650).

The NewYork-Presbyterian/Weill Cornell investigation, led by Dr. Altorki, looked at 29 patients with non-small-cell lung cancer who

with grade 3-4 neutropenia seen in 18 patients (62%). There were no complete pathologic responses among the 28 patients who underwent complete tumor resection, but 7 patients (24%) did have minimal residual microscopic disease.

Investigators measured levels of PGE₂ in 17 study subjects and 13 controls—patients who received preoperative paclitaxel-carboplatin but no celecoxib. In controls, levels of PGE₂ markedly increased after treatment with paclitaxel and carboplatin. In contrast, the increase in PGE₂ levels was abrogated in the study subjects who received celecoxib in addition to the chemotherapy.

In an upcoming confirmatory

Novel Therapies for Polycythemia vera

How blood cells develop and react with the rest of the cells in the body is critical to understanding the biology of myeloproliferative diseases such as polycythemia vera.

Recent research led by Richard Silver, MD, at the Center for Leukemia and Myeloproliferative Disorders at NewYork-Presbyterian Hospital and Weill Medical College of Cornell University, has centered around new treatments—including alternative therapies—for polycythemia vera, an uncommon (but progressive and often fatal) disease characterized by red blood cell and megakaryocyte overproduction. The work has focused on the use of imatinib mesylate, the protein tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia, as well as interferon therapy.

According to Dr. Silver, *in vitro* studies have shown that interferon inhibits both red blood cell and megakaryocyte overproduction. Inhibiting red blood cell overproduction obviates the need for phlebotomy. In addition, the inhibition of megakaryocytic proliferation and the resulting cytokine release can limit the progression of fibrosis.

Recognizing that the study of myeloproliferative disorders has been underfunded, Congress recently mandated an increase in money available for research in this area. To this end, an international consortium for the study of myeloproliferative disorders has been developed. The consortium participants include researchers from medical centers worldwide.

Traditionally, polycythemia vera has been treated with phlebotomy and the myelosuppressive agent hydroxyurea, which can be leukemogenic. It can also cause many side effects, including skin ulcers. Even with myelosuppressive therapy, polycythemia vera progresses to myelofibrosis (scarring of the bone marrow) and increasing splenomegaly.

But since Dr. Silver's initial reports of interferon treatment for the disease, its use in trials worldwide has increased. His trials, conducted over the past 15 years at NewYork-Presbyterian/Weill Cornell, and published in journals such as *Blood* (1999;94:1517-1536), *Annals of Internal Medicine* (1993;119:1091-1092), and *The Lancet* (1988;2:403), have shown interferon to be safe and very effective.

In the published data, patients were started on 1 million units of interferon alfa-2b 3 times weekly, which was increased to 3 million units 3 times weekly. Doses were adjusted according to tolerance. "Our goals were to reduce the platelet count to normal, to make the patient phlebotomy-free, and to

reduce the spleen size," Dr. Silver explained. These goals have been achieved in all of the patients Dr. Silver has treated with interferon, and none has suffered thrombosis or developed leukemia.

"Interferon has been extremely effective in preventing the morbidity and mortality of [polycythemia vera]," said

Dr. Silver. "However, a few patients—about 10%—have developed side effects requiring its discontinuation."

Treating polycythemia vera patients with imatinib has also proven effective. Although the disease is not caused by a specific molecular abnormality like Bcr-Abl in chronic myeloid leukemia but by a broader, still unknown genetic abnormality, there is a strong rationale for the use of imatinib in patients suffering from the

"Interferon has been extremely effective in preventing the morbidity and mortality of [polycythemia vera]. However, a few patients—about 10%—have developed side effects requiring its discontinuation."

—Richard Silver, MD

disease. Stem cell factor is an essential element for erythroid progenitor cell proliferation and differentiation in polycythemia vera. Stem cell factor signals by inducing tyrosine phosphorylation of its c-kit receptor, which may also affect the erythropoietin receptor. Imatinib is known to block stem cell factor signaling through c-kit. Thus, it was considered possible that imatinib could inhibit autonomous erythropoiesis of polycythemia vera.

In the June 2003 issue of *Leukemia* (2003;17:1186-1187), Dr. Silver reported on a trial of 7 patients that was presented at the American Society of Hematology meeting in December 2002. In the article, he showed that imatinib is effective in reducing red blood cell count, greatly reducing or eliminating the need for phlebotomy, and reducing spleen size. However, further investigation is warranted to determine long-term response, optimum dose, and side effects of imatinib therapy for polycythemia vera. An ongoing cooperative trial will further evaluate imatinib treatment. This trial involves medical centers across the country.

Recognizing that the study of

see [Polycythemia vera](#), page 11

Advances in the Treatment of Neuroblastoma

A new treatment for neuroblastoma, the most common solid pediatric tumor, is under investigation at Morgan Stanley Children's Hospital of NewYork-Presbyterian and Columbia University College of Physicians & Surgeons. Neuroblastoma strikes about 600 infants and children each year in the United States, with most having metastatic disease at the time of diagnosis. Only 30% to 35% survive for 5 years despite treatment with intensive chemotherapy, followed by autologous stem cell transplantation.

A new approach, which incorporates allogeneic cellular immunotherapy into a standard treatment protocol, is being evaluated by Darrell Yamashiro, MD, PhD, and co-workers at the Morgan Stanley Children's Hospital of NewYork-Presbyterian.

Treatment consists of 4 phases. In the induction phase, 6 cycles of intensive multiagent chemotherapy are given. Dexrazoxane and amifostine are given for cardioprotection and renal protection, respectively, with surgery performed for local tumor control. The patient's own stem cells, collected after the second cycle of intensive chemotherapy and purged of residual tumor cells, are transplanted back during the second, consolidation phase of the treatment.

In the immunotherapy phase, performed 2 to 3 months after autologous transplantation, neuroblastoma patients receive reduced-intensity (nonmyeloablative) chemotherapy, followed by allogeneic stem cell transplantation. The source of stem cells depends on whether a suitable donor is available.

Induction Phase

ZVAC	Z Zinecard Day 0, 1 V Vincristine Day 0 A Adriamycin Day 0, 1 C Cyclophosphamide Day 0, 1
ACiE	A Amifostine Day 0, 1, 2, 3 Ci Cisplatin Day 0, 1, 2, 3 E Etopophos Day 0, 1, 2

Consolidation Phase

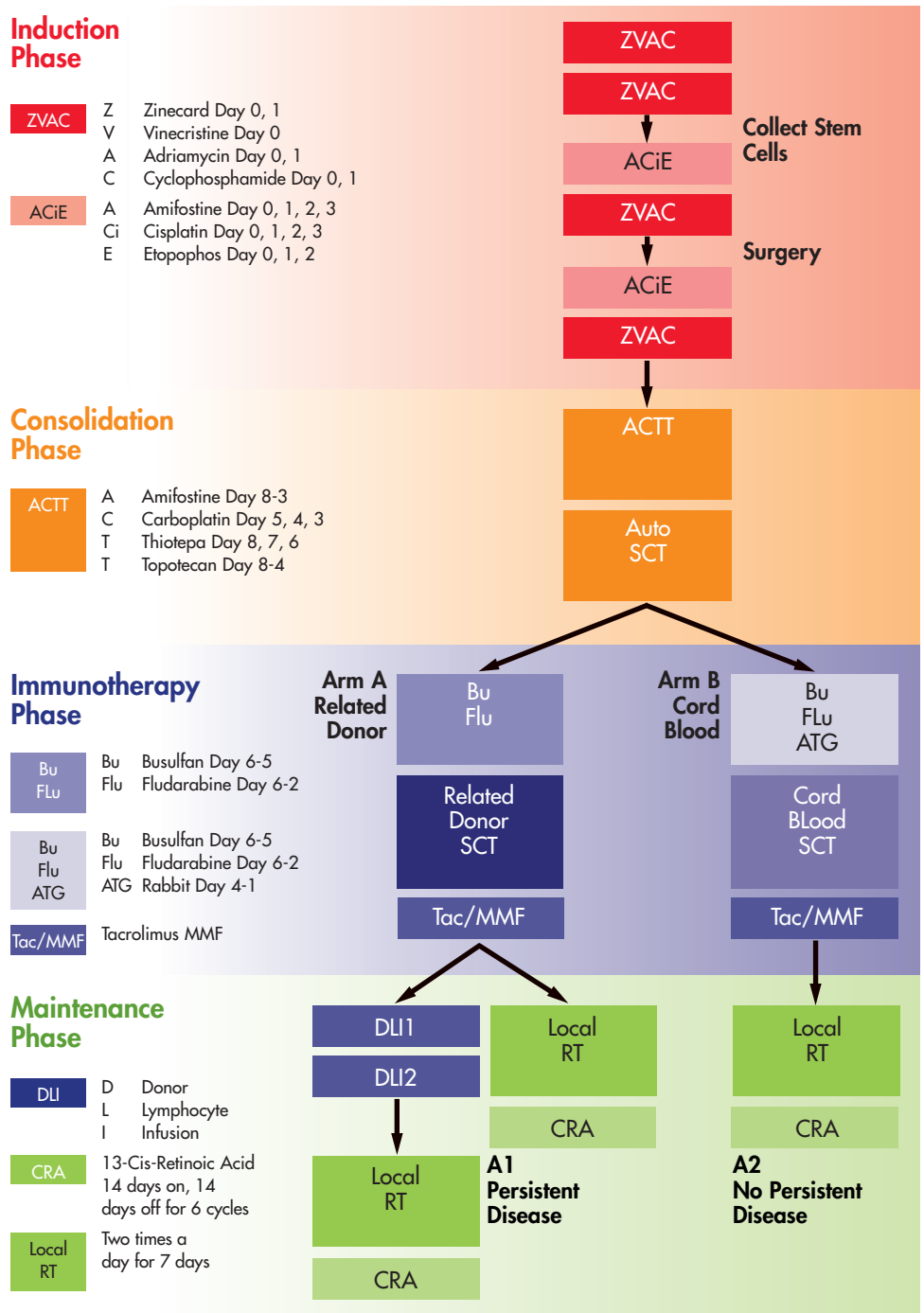
ACTT	A Amifostine Day 8-3 C Carboplatin Day 5, 4, 3 T Thiotepa Day 8, 7, 6 T Topotecan Day 8-4
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Immunotherapy Phase

Bu Flu	Bu Busulfan Day 6-5 Flu Fludarabine Day 6-2
Bu Flu ATG	Bu Busulfan Day 6-5 Flu Fludarabine Day 6-2 ATG Rabbit Day 4-1
Tac/MMF	Tacrolimus MMF

Maintenance Phase

DLI	D Donor L Lymphocyte I Infusion
CRA	13-Cis-Retinoic Acid 14 days on, 14 days off for 6 cycles
Local RT	Two times a day for 7 days



Researchers at Morgan Stanley Children's Hospital of NewYork-Presbyterian are investigating a new treatment approach to neuroblastoma that consists of 4 phases: 1) induction phase, in which 6 cycles of intensive multiagent chemotherapy are given; 2) consolidation phase, in which the patient's own stem cells, collected after intensive chemotherapy and purged of residual tumor cells, are retransplanted; 3) immunotherapy phase, in which patients receive reduced-intensity (nonmyeloablative) chemotherapy, followed by allogeneic stem cell transplantation; and 4) maintenance phase, in which patients with no response to the donor stem cell transplant receive therapy for minimal residual disease with low-dose irradiation, followed by 13-cis-retinoic acid.

Patients with no suitable donor receive a cord-blood stem cell transplant. Along with the transplant, immunosuppressive agents are given to prevent graft-versus-host disease.

The rationale for the technique, demonstrated by Childs et al (*N Engl J Med* 2000;343:750-758), is that it will induce a graft-versus-tumor effect. "The patient's own immune system cannot recognize the tumor, but by adding what is essentially a new immune system, we hope to see destruction of the tumor," Dr. Yamashiro said.

In the maintenance phase, patients with no response to the donor stem cell transplant will receive 2 infusions of donor lymphocytes. All patients still enrolled will receive therapy for minimal residual disease with low-dose irradiation, followed by 13-cis-retinoic acid, a vitamin A analog known to

decrease proliferation and differentiation in neuroblastoma cell lines, which may show efficacy against minimal residual disease.

"By treating with nonmyeloablative chemotherapy just prior to allogeneic transplantation, there is a gradual replacement of bone marrow by the new donor cells," Dr. Yamashiro said, adding, "A major benefit of this technique is that there are fewer side effects." This and other ongoing studies at Morgan Stanley Children's Hospital

of NewYork-Presbyterian should provide the basis for large-scale trials of immunotherapy in patients with appropriate tumor types.

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"The patient's own immune system cannot recognize the tumor, but by adding what is essentially a new immune system, we hope to see destruction of the tumor."

—Darrell Yamashiro, MD, PhD

Polycythemia vera

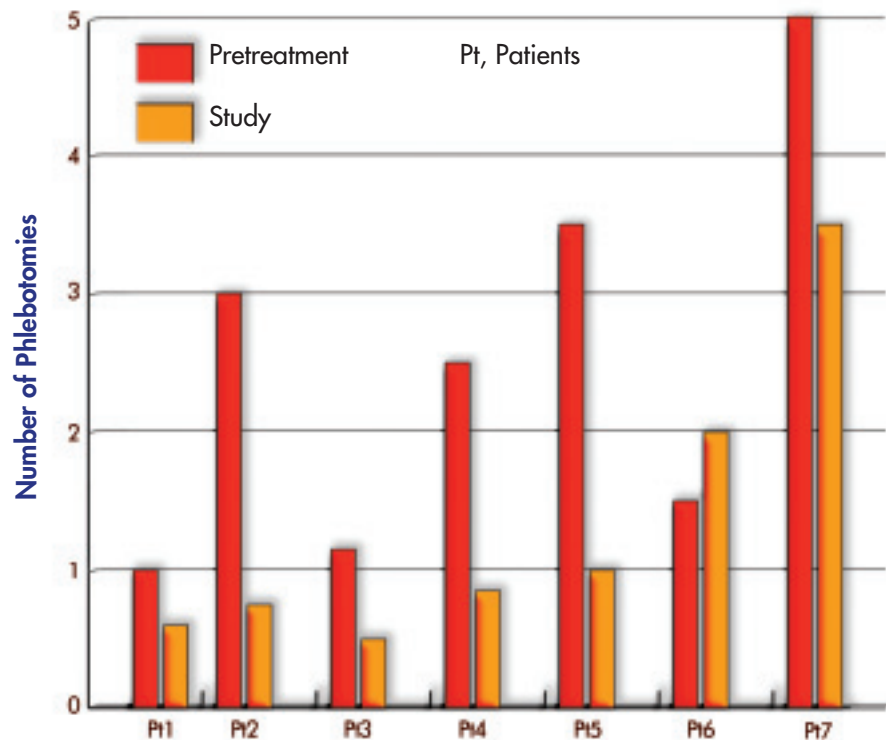
continued from page 9

myeloproliferative disorders has been underfunded, Congress recently mandated an increase in money available for research in this area. To this end, an international consortium for the study of myeloproliferative disorders has been developed; Dr. Silver is a member of its executive committee. The consortium participants include researchers from medical centers worldwide.

Further studies will determine the best treatment, or combination of treatments, for polycythemia vera. "Perhaps a combination of both imatinib mesylate and interferon might be workable, but that's something in the future," said Dr. Silver.

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Imatinib mesylate reduces phlebotomy requirements in polycythemia vera



A study by Richard Silver, MD, of NewYork-Presbyterian/Weill Cornell examined the change in phlebotomy requirements for 3-month periods before and during imatinib mesylate therapy. In all, 6 of 7 patients in the study required fewer phlebotomies after initiation of imatinib therapy. For full study results, see *Leukemia* (2003;17:1186-1187).

Melanoma

continued from page 7

fighting melanomas that have metastasized to the brain. A significant number of patients undergoing the treatment have outlived their initial prognoses. In another effort, researchers are currently using molecular profiling to determine why 20% of patients respond to treatment with the protein.

“If we can do that, we might be able to increase the immune responses or even predict which patients will benefit,” said Dr. Kaufman.

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