A clinical trial for a potential pancreatic cancer vaccine

Stereotactic body radiation therapy used to target liver cancer

A minimally invasive option for esophageal cancer
Cancer Center Set to Open

This issue of UH Innovations in Surgery spotlights the work of surgeons at University Hospitals Case Medical Center who use cutting-edge therapies and techniques to treat patients with pancreatic cancer, melanoma, liver cancer and esophageal cancer. As you will read, in addition to their expertise in the most advanced surgical techniques, many of our oncology surgeons are also leaders in clinical studies of investigational immunotherapies and stereotactic body radiation therapy for patients with cancer.

Also in this issue, we have the pleasure of announcing that in recognition of Jane and Lee Seidman’s unprecedentedly generous $42 million donation, UH is naming our new freestanding cancer hospital and our integrated regional network of nine outpatient cancer programs the Jane and Lee Seidman Cancer Center. The new cancer hospital is scheduled to open in spring 2011 on the UH Case Medical Center campus. This $260 million, 375,000-square-foot, 120-bed facility will triple the square footage that cancer services currently encompass at UH Case Medical Center and will integrate all facets of cancer care under one roof.

The UH Seidman Cancer Center builds on the legacy established by the late R. Livingston Ireland Jr., a UH Case Medical Center board member who lobbied vigorously for significant state funding to further UH’s cancer program in the early 1980s. In recognition of Mr. Ireland’s successful efforts the Cancer Center was named in his honor. A lasting tribute will be displayed prominently in the UH Seidman Cancer Center.

The four state-of-the-art surgical suites housed in this new facility are being specifically designed and equipped to further augment our surgeons’ ability to safely and effectively perform the most advanced image-guided and minimally invasive techniques. Also, the UH Seidman Cancer Center will be the first cancer center in the world to offer patients access to PET/MRI, and will feature one of just a few intraoperative magnetic resonance imaging (iMRI) chambers in Northern Ohio.

Sincerely,

Jeffrey L. Ponsky, MD, FACS
Surgeon-in-Chief,
University Hospitals Case Medical Center
Oliver H. Payne Professor and Chairman,
Department of Surgery
Case Western Reserve University School of Medicine
Pancreatic Cancer Vaccine: A Closer Look

Immunotherapeutic vaccine approach exploits difference between humans and other mammals

**Jeffrey Hardacre, MD**, Section Head, Pancreatic Surgery, Seidman Cancer Center, University Hospitals Case Medical Center, and Assistant Professor of Surgery, Case Western Reserve University School of Medicine, is a principal investigator for a Phase III clinical trial testing the HyperAcute-Pancreas vaccine in patients with pancreatic cancer (see sidebar).

NewLink Genetics, the company sponsoring this clinical study, is also developing HyperAcute vaccines for lung cancer, melanoma and prostate cancer, all based on the concept of hyperacute rejection. “This is the process that is responsible for humans not being able to receive transplants from other mammals,” explains Dr. Hardacre.

**MECHANISM OF ACTION**

The basis for hyperacute rejection of mammalian xenotransplants is the presence of alpha-1,3-galactosyl (alpha-gal) carbohydrate residues bound to the cell surface lipids and proteins of all mammals, except humans and Old World primates. Because the intestinal flora in humans is rich in alpha-gal, up to 1 percent of our circulating IgG antibodies recognize this molecule.

“The scientists at NewLink Genetics have isolated human pancreatic cancer cells, grown them in culture, and made them express alpha-gal. These cells are terminally sterilized so that they cannot grow as a cancer when given to a patient. These altered human pancreatic cancer cells are given as a vaccine,” says Dr. Hardacre. The theory is that the immune system of vaccinated patients will recognize these injected cells as abnormal, triggering an immune response against the inoculum and also against the patients’ endogenous pancreatic cells.

**PRELIMINARY RESULTS**

While studies with the HyperAcute-Pancreatic vaccine have yet to be published, preliminary data have been presented at the recent annual meeting of the American Society of Clinical Oncology (ASCO). In preclinical studies, the vaccine exhibited a good safety profile and a suggestion of lessening of tumor burden, says Dr. Hardacre. In a Phase I study in patients with metastatic pancreatic cancer, there were no serious side effects associated with the vaccine.

In an abstract for the ASCO 2011 Gastrointestinal Cancers Symposium (Jan. 20-22, San Francisco, California), Dr. Hardacre and co-authors summarized an interim analysis of data from a Phase II study of the HyperAcute vaccine administered in conjunction with standard adjuvant therapy (chemotherapy plus chemoradiation therapy) given for six months after surgery to 73 patients with resectable pancreatic cancer. With median follow-up of 15 months, estimated Kaplan-Meier survival rates were 91 percent at 12 months and 54 percent at 24 months. According to Dr. Hardacre, the 16-month primary endpoint of median disease-free survival compares favorably with 11 to 13 months reported in prospective randomized Phase III studies of standard adjuvant therapy. A longer follow-up is needed to finalize the results of this study.

“The main toxicities related to the vaccine have been injection site reactions marked by pain, redness and swelling,” Dr. Hardacre says. “Main toxicities associated with the adjuvant therapy are what would be expected for standard chemotherapy and radiation.”

**Phase III Clinical Trial Open for Enrollment**

With Jeffrey Hardacre, MD, as a principal investigator, UH Seidman Cancer Center is currently recruiting participants in a prospective, multicenter randomized Phase III study (ClinicalTrials.gov, identifier: NCT01072981) of HyperAcute-Pancreas vaccine compared with no vaccine given in addition to standard adjuvant therapy, consisting of chemotherapy alone or chemotherapy with chemoradiation therapy.

- Adults with surgically resected (R0 or R1), stage 1 or 2 pathology-confirmed adenocarcinoma of the pancreas are eligible for this study.
- The primary study endpoint is overall survival.

**Trial Information**

To learn more about this trial, contact Jeffrey Hardacre, MD, at 216-844-7047, option #2, or Jeffrey.Hardacre@UHhospitals.org, or Robert Sprosty at 216-844-7026 or Robert.Sprosty@UHhospitals.org.
Investigating Immunotherapy for Melanoma

Surgeon leads multidisciplinary collaborations in search of novel therapeutic approaches for metastatic melanoma

At Seidman Cancer Center, University Hospitals Case Medical Center, surgeons are at the vanguard of their surgical specialties, but they also are involved in cutting-edge research for systemic therapies for the treatment of metastatic melanoma.

"Surgeons are doing more than just operating on patients with robots, lasers and other sophisticated equipment," says Julian Kim, MD, Chief, Oncologic Surgery, UH Seidman Cancer Center, and Charles A. Hubay Professor of Surgery, Case Western Reserve University School of Medicine. Despite many advances in surgeons' ability to resect tumors, aggressive cancers like melanoma quickly spread to other organs. Systemic therapy is needed to circulate through the bloodstream and kill cancer at multiple metastatic sites. To attack the problem of metastatic melanoma beyond surgery, Dr. Kim has been investigating ways to develop immunotherapies that would boost a patient's immune response to the cancerous cells. His two main areas of research are vaccine immunotherapy and adoptive immunotherapy.

VACCINE GENE THERAPY

Under Dr. Kim's leadership, the UH Seidman Cancer Center is the only melanoma center in Northern Ohio involved in a company-sponsored, international, multicenter, randomized Phase III clinical trial of the investigational vaccine Allovectin-7. Allovectin-7 is a plasmid/lipid complex containing artificial genes that encode human leukocyte antigen (HLA)-B7 and B2microglobulin, which together form a major histocompatibility complex, class I. This vaccine is directly injected into melanoma tumors in skin, where expression of the artificial genes is thought to make the melanoma cells recognizable by the patient's immune system, explains Dr. Kim.

"The beauty of any treatment that boosts the immune system," he says, "is that if you generate an immune response to one cancer at one particular site, the same immune cells can circulate through the bloodstream and kill similar cancers at other sites that haven't been injected by that gene."

In the Phase III study, patients with stage 3 or 4 melanoma have been randomized to treatment with Allovectin-7 or standard chemotherapy with dacarbazine or temozolomide. Patient accrual is complete and outcome data are being collected. If this study shows a positive effect of the Allovectin-7 therapy, the manufacturing company will submit the data to the FDA.

ADOPTIVE IMMUNOTHERAPY

Dr. Kim is also principal investigator of his own adoptive immunotherapy research project funded by a grant from the National Institutes of Health. In adoptive immunotherapy immune cells are removed from a patient, activated and expanded in culture, and re-infused into the patient to treat his or her cancer.

Currently, Dr. Kim and his team are working on optimizing the method and reagents to grow and activate immune cells in culture. They take portions of lymph nodes from patients who are having their lymph nodes removed during routine melanoma surgery. These lymph nodes are tested in the laboratory using a variety of cytokines and other activating chemicals. After these studies are successfully completed, Dr. Kim plans to submit an Investigational New Drug Application to the FDA to perform a clinical trial in patients.

There is only a small number of centers in the world that do this type of T-cell therapy, explains Dr. Kim. Most of these centers will use a patient's peripheral blood cells or immune cells that are isolated from an actual tumor specimen as the starting material for cell isolation. In Dr. Kim's studies they use lymph nodes because: (1) they are a highly concentrated source of immune cells; and (2) lymph nodes are the body's natural way of stimulating T-cells to recognize foreign antigens such as those expressed by bacteria. “We thought it was best to start with lymph nodes as the starting material because there would be immune cells within the lymph nodes already aimed against the cancer," says Dr. Kim.

Dr. Kim and his research group have been working on this adoptive immune therapy project for the past four years. He is fairly optimistic that in the next year to 18 months, his group will get approval to start a clinical trial.

GOING ABOVE AND BEYOND SURGERY

Part of the reason that Dr. Kim can do these research studies is that he collaborates with a medical oncologist, Henry Koon, MD, Disease Team Leader, Melanoma, UH Seidman Cancer Center, and Assistant Professor, Case Western Reserve University School of Medicine. Despite many advances in surgeons' ability to resect tumors, aggressive cancers like melanoma quickly spread to other organs. Systemic therapy is needed to circulate through the bloodstream and kill cancer at multiple metastatic sites. To attack the problem of metastatic melanoma beyond surgery, Dr. Kim has been investigating ways to develop immunotherapies that would boost a patient's immune response to the cancerous cells. His two main areas of research are vaccine immunotherapy and adoptive immunotherapy.

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Western Reserve University School of Medicine, who shares a strong interest in immunotherapy.

“We do a lot of complicated surgery here for melanoma. We are involved with the newest surgical techniques,” says Dr. Kim. “But really, our focus is to go beyond surgery and to think of ways to actually eradicate metastatic melanoma. These two trials are examples of development of new treatments for melanoma based on stimulation of the immune system.”

State-of-the-Art Melanoma Treatments

Henry Koon, MD, has brought to UH Seidman Cancer Center two important types of treatment for patients with metastatic melanoma: interleukin-2 and ipilimumab.

Interleukin-2 is a cytokine approved by the FDA that produces tumor shrinkage in about 20 percent of patients. Interleukin-2 antitumor activity is dependent on the patient’s immune system to kill melanoma – the drug itself has no cytotoxic effect on melanoma cells. This is a complicated treatment that requires hospitalization, explains Julian Kim, MD.

Ipilimumab is a monoclonal antibody to CTLA4, an inhibitory immune molecule that turns off T-cell activation in the body. Dr. Kim explains that blocking CTLA4 activation is thought to improve the immune system’s ability to fight melanoma. In a Phase III study presented at the 2010 annual meeting of the American Society of Clinical Oncology, treatment with ipilimumab improved survival in patients with metastatic melanoma. Dr. Koon was the principal investigator for this trial at UH Seidman Cancer Center. UH Seidman Cancer Center is the only center in Northern Ohio that has a compassionate use protocol for ipilimumab to allow patients to receive this treatment while it is under review by the FDA.

For more information about immunotherapy for melanoma offered at UH Seidman Cancer Center, contact Dr. Kim at 216-844-8247, option #2, or Julian.Kim@UHhospital.org.
Stereotactic Body Radiation Therapy

Precision-delivered ablative radiation therapy for patients with non-resectable primary or secondary liver cancers

Traditional radiation therapy can damage a widely scattered field, involving skin and other healthy tissue surrounding a target lesion. In contrast, stereotactic body radiation therapy (SBRT) provides laser-like targeting of ablative doses of radiation.

"Using SBRT, we can precisely deliver very high radiation doses with computers to monitor tumor movement associated with respiration. We have been able to treat patients who were in hospice expecting to die within a couple of months, providing them with one or two years of good quality life," says Juan Sanabria, MD, Surgeon, University Hospitals Case Medical Center, and Assistant Professor of Surgery, Case Western Reserve University School of Medicine.

**PROMISING CLINICAL STUDIES**

Dr. Sanabria and colleagues at UH Case Medical Center recently published in *HBP Surgery* (pii: 309780; Epub 2010 June 28) preliminary results of a clinical trial of SBRT in patients with non-resectable liver tumors. They found that SBRT led to local control in 82 percent of all patients enrolled in the study, including 100 percent of patients with hepatocellular carcinoma. Collaborators from Memorial Sloan-Kettering Cancer Center, the University of Rochester in New York, and Cleveland Clinic have found that these findings were reproducible.

Dr. Sanabria's team at UH Case Medical Center and investigators from these other institutions are now collaborating in clinical research to see if SBRT could be used to downstage hepatocellular carcinoma. A Phase II study is currently open for enrollment (see sidebar) and a Phase III randomized trial will follow.

**CAREFULLY PLANNED TREATMENT**

Dr. Sanabria explains that planning of treatment can take up to four weeks, during which time patients are evaluated by a hepatobiliary/transplant surgeon, a medical oncologist, a hepatologist and a radiation oncologist. Patients undergo staging CT, MRI or PET imaging studies. A handful of 3-5 mm cylindrical solid gold fiducial markers are placed surgically or subcutaneously (with CT guidance) within or around the lesion. Additional MRI and CT scans are used to contour the target and carefully plan how the radiation will be delivered. SBRT is given over the course of two hours during three consecutive days.

Some patients have experienced weakness, but no other significant side effects have been reported, says Dr. Sanabria.

SBRT is not offered by many institutions because it requires a large investment in equipment, installation, maintenance and trained personnel. At UH Case Medical Center, SBRT delivered via the CyberKnife® system is performed within the auspices of two study protocols to provide more coordinated patient care and follow-up. This is an FDA-approved procedure that is covered by insurance.

**Phase II Study Open for Enrollment**

With Juan Sanabria, MD, as the principal investigator, UH Seidman Cancer Center is currently recruiting participants in a Phase II study of SBRT (ClinicalTrials.gov, identifier: NCT01194206).

- Adults with hepatocellular carcinoma or cholangiocarcinoma considered non-resectable and not eligible for transplantation may be considered for this study.
- This study will assess the rate of downstaging of hepatocellular carcinoma at three months following SBRT.

**Trial Information**

To learn more about this trial or to ask about stereotactic body radiation therapy for your patients with liver cancer, contact Juan Sanabria, MD, at 216-844-3138, option #2, or Juan.Sanabria@UHhospitals.org.
A 55-year-old man presented with dysphagia. After an esophagoscopy, the patient was referred to University Hospitals Case Medical Center, where he underwent an endoscopic ultrasound and additional staging procedures. The patient was diagnosed with distal esophageal cancer, T2 N0 M0. In the absence of local or distant metastases, he was deemed a primary surgical candidate for esophageal resection.

TREATMENT
The patient underwent a minimally invasive laparoscopic/thoracoscopic Ivor-Lewis esophagectomy. The surgeons used a laparoscopic approach through the abdomen to fashion a gastric tube using the stomach. A jejunal feeding tube was also placed and the pylorus was injected with botulinum toxin to prevent delayed gastric emptying. The thoracic part of the operation involved a subtotal esophagectomy, a proximal gastrectomy, pull-up and anastomosis of the newly devised gastric tube.

Postoperatively, the patient developed a minor anastomotic leak, which was treated with a temporary removable esophageal stent. The patient was discharged on a regular diet. At his five-week postoperative office visit, the patient was doing well, eating without difficulty, and his feeding tube was removed.

DISCUSSION
“As far as we know, this was the first minimally invasive Ivor-Lewis esophagectomy performed in Northern Ohio,” explains Carsten Schroeder, MD, PhD, Attending Surgeon, UH Case Medical Center, and Assistant Professor of Surgery, Case Western Reserve University School of Medicine. “There are three types of procedures used to perform open or minimally invasive esophagectomy: (1) Ivor-Lewis esophagectomy; (2) three-field esophagectomy; and (3) transhiatal esophagectomy. Surgeons at UH Case Medical Center can do all three types of operations using a minimally invasive approach,” says Dr. Schroeder. “All of these options are available and are tailored to the patient’s needs and disease location. No single approach fits all.

“At seven hours, laparoscopic Ivor-Lewis takes longer than the classic operation, which averages five hours,” says Dr. Schroeder, “but the recovery period and pain are significantly reduced.” The minimally invasive procedure is performed using several small incisions in the lateral chest and the upper abdomen. By contrast, the open surgery involves a 20 to 25 cm incision in the abdomen and another large 25 cm incision in the chest.

With the minimally invasive approach, explains Dr. Schroeder, “patients have less pain, faster mobilization and, if there are no complications, they will have a faster recovery and a shorter hospital stay.”

Complications with this type of difficult operation, however, are a common problem, cautions Dr. Schroeder. He estimates that nationwide, 10 to 15 percent of patients who undergo open or laparoscopic esophagectomy will have an anastomotic leak and the morbidity rate is about 30 percent.

“Patients normally appreciate that we try a more minimally invasive approach to avoid the large incisions for pain, recovery and cosmetic reasons,” says Dr. Schroeder.

Dr. Schroeder and Michael J. Rosen, MD, Division Chief, General Surgery, UH Case Medical Center, and Associate Professor, Case Western Reserve University School of Medicine, collaborate with gastroenterologists Amitabh Chak, MD, Gastroenterology, UH Case Medical Center, and Professor, Case Western Reserve University School of Medicine, and Ashley L. Faulx, MD, Gastroenterology, UH Case Medical Center, and Assistant Professor, Case Western Reserve University School of Medicine, as well as other specialists at UH Case Medical Center to provide an optimal comprehensive team approach for the treatment of patients with esophageal cancer.
In spring 2011, a new $260 million, 375,000-square-foot, 120-bed cancer hospital will open on the University Hospitals Case Medical Center campus. This freestanding facility and UH’s integrated regional network of nine outpatient cancer programs will comprise the newly named UH Jane and Lee Seidman Cancer Center. The new facility will be the first cancer center in the world to offer access to PET/MRI machines, and will have four operating rooms specifically designed and equipped to facilitate the application of the latest image-guided and minimally invasive techniques for the treatment of patients with solid tumors.

**INTRAOPERATIVE MRI**

One of the operating rooms will provide direct access to an intraoperative magnetic resonance imaging (iMRI) scanner.

“The most common application for iMRI in our surgical suite will be for patients with brain tumors,” says Julian Kim, MD, Chief, Oncologic Surgery, UH Seidman Cancer Center, and Charles A. Hubay Professor of Surgery, Case Western Reserve University School of Medicine. In brain surgery, surgeons must strike a balance between removing all of the tumor and sparing as much normal tissue as possible.

“The reality is that despite a surgeon’s best effort, in about 30 percent of patients who have undergone a curative resection postoperative MRI will show some residual tumor,” notes Dr. Kim. “It’s not by any fault of the surgeon. It’s the nature of brain tumor surgery.”

In the iMRI suite, patients under anesthesia with the brain exposed will undergo imaging under sterile conditions, allowing surgeons to excise residual tumor identified during the scan. The application of iMRI has the potential to improve patient outcomes by facilitating more complete tumor resection and sparing patients a second operation to remove remaining malignant tissue.

In addition to a specialized chamber built in or adjacent to the operating room, iMRI requires the use of specialized non-metal-containing, MRI-compatible equipment, such as the anesthesia machine and surgical retractors, which will be wheeled with the patient in the imaging chamber.

“Making sure that all the safety checks are in place takes a lot of resources and careful planning,” explains Dr. Kim. “Not many hospitals in the United States have this type of technology.”

**MINIMALLY INVASIVE TECHNOLOGIES**

In the other operating rooms in the UH Seidman Cancer Center, there will be an emphasis on the most advanced, minimally invasive surgical technologies. Surgeons will also work closely with the interventional radiology group and the radiation oncology group to maximize the use of minimally invasive, ablation techniques such as robotic radiosurgery, ultrasound wave tumor ablation and radiofrequency tumor ablation. The availability of the iMRI suite will facilitate the use of these ablation techniques by allowing real-time monitoring of their effectiveness.

To learn more about the UH Seidman Cancer Center, visit UHSeidman.org.

**Your Feedback Is Important**

As a medical professional, your input is invaluable in helping us shape future issues of UH Innovations in Surgery. We want to know what’s important to you. Do you want to read about cutting-edge research, learn about the latest technology, or hear firsthand case studies of how others in your specialty are improving and saving lives? Tell us what you want to read about and your name will be entered to win one of two Apple iPads! Simply visit UHhospitals.org/innovations.