If you get it, you die of it.” That’s the traditional view regarding pancreatic cancer, and by and large, that view has been justified. Although pancreatic cancer ranks 10th in men and 11th in women in incidence among cancers, it ranks 4th in cancer-related deaths, and the 5-year overall survival rate is only 5%.

But within the past few years, significant progress has been made in helping patients with operable disease. Further, recent insights into pancreatic cancer have led to clinical trials of a range of new treatment approaches for patients with advanced disease.

The reasons that pancreatic cancer presents such a challenge are well known. First, it is almost always diagnosed after it has spread. Patients tend to present with vague symptoms—for example, gastrointestinal distress or pain—that more commonly arise from other cancers. Such tactics appear to slowly be turning the tide against this difficult tumor.

(Continued on page 2)
medical conditions such as gallstones, ulcers, or reflux. By the time these symptoms have developed and other causes have been excluded, the cancer is often locally advanced or metastatic, at which point the likelihood of surviving the disease drops dramatically.

A second reason that pancreatic cancer is challenging is that surgery—the treatment option that, when feasible, gives the best prognosis—is often precluded by the complexity of the anatomy in the area, the extent of disease, and the older age of many patients. Only 10%–15% of patients are able to undergo surgery.

For patients who can’t undergo surgery, chemotherapy (usually with gemcitabine [Gemzar]) is part of the standard treatment. But these patients face a third reason that pancreatic cancer is so challenging: even if tumors respond to gemcitabine initially, almost all rapidly become resistant to the drug.

Together, these reasons explain why most patients diagnosed with pancreatic cancer die within the first year—and hence, pancreatic cancer’s historically dismal reputation.

What’s encouraging today is that there are a number of new approaches to pancreatic cancer treatment, according to James L. Abbruzzese, M.D., a professor in and chair of the Department of Gastrointestinal Medical Oncology at The University of Texas M.D. Anderson Cancer Center. Some of these approaches—such as a new strategy for multidisciplinary care for operable disease—have been demonstrated to be effective, and others—such as new types of anticancer agents—are being tested in clinical trials at M. D. Anderson. These strategies approach the disease from many angles, with many mechanisms of action. “We’re trying to be as comprehensive as we can,” Dr. Abbruzzese said.

**Timing surgery for better results**

In the United States, most patients with resectable pancreatic cancer undergo surgery as their first treatment and then receive systemic chemotherapy or chemoradiation. At M. D. Anderson, however, many patients are being treated on protocols that involve chemotherapy or chemoradiation first and then surgery. Clinicians are excited about the increased survival durations they’ve obtained with this approach.

Initial studies of this treatment approach have shown benefits for two groups of patients. For patients with resectable cancers, two phase II trials with a total of 176 patients have been completed. In one trial, patients received gemcitabine and radiation before pancreaticoduodenectomy; in the second, patients received gemcitabine and cisplatin, then gemcitabine and radiation, before surgery. The median overall survival durations in the patients who completed treatment were 34 months in the first trial and 31 months in the second.

Some patients with borderline resectable cancers—those who were not clear candidates for surgery initially because of the extent or location of disease—also benefited from this treatment strategy, the M. D. Anderson team found. One hundred sixty such patients were enrolled in a trial of chemotherapy or chemoradiation as initial therapy. In the 66 patients whose tumors were clearly operable after systemic therapy, the median survival duration was 40 months. “We’re really starting to see some tangible improvements,” said Dr. Abbruzzese.
Catching Pancreatic Cancer Early

While researchers refine treatment strategies, they’re also working on screening strategies. “The long-term approach in dealing with pancreatic cancer is going to be in prevention and earlier detection,” said Dr. Abbruzzese. “If we could detect the disease very early, some of our currently available therapies would be much, much more effective.”

Currently, the trigger for performing diagnostic studies is the development of symptoms, such as jaundice, abdominal or back pain, digestive issues, a change in urine or stool color, or the sudden onset of diabetes. But because symptoms usually develop after the disease has progressed, early detection is rare. Improving early-detection rates would mean screening asymptomatic patients.

What type of screening strategy would be practical? Because of the rarity of pancreatic cancer, mass screening of the public would not be reasonable. However, screening of those at increased risk for the disease would be worthwhile. One such group is people who have a mutation of the BRCA2 gene or who have multiple family members who’ve developed pancreatic cancer. This group is eligible now for an M. D. Anderson clinical trial that examines whether a combination of imaging modalities (endoscopic ultrasonography, computed tomography, and magnetic resonance imaging or magnetic resonance cholangiopancreatography) can detect early-stage disease.

In the lab, M. D. Anderson researchers are looking for biomarkers of early-stage pancreatic cancer or, better yet, of its precursor, pancreatic intraepithelial neoplasia (PanIN). What would be ideal, said Dr. Logsdon, is a biomarker that identifies PanIN 3, the last stage of PanIN before malignant transformation occurs. Further, the ideal biomarker would distinguish PanIN 3 from chronic pancreatitis, a more common, benign disease (the best biomarker thus far, CA19-9, is elevated in both pancreatic cancer and chronic pancreatitis).

Two recent advances are going to help Dr. Logsdon and colleagues in their search. First, they’ve created a mouse model in which PanIN develops and transforms into pancreatic cancer. This model provides the opportunity to look at early-stage disease, which is hard to do in humans because pancreatic cancer is usually found so late.

The second advance is a new assay, developed in conjunction with Gordon B. Mills, M.D., Ph.D., chair of the Department of Systems Biology at M. D. Anderson, that will make the testing of candidate biomarkers much more feasible. The standard testing method, enzyme-linked immunosorbent assay, requires a fairly high volume of blood (50–100 mL) and the use of two antibodies, which is expensive. The new reverse-phase protein array (RPPA) requires only 1 mL of blood and one antibody. The RPPA will now enable Dr. Logsdon to test a panel of 20 candidate biomarkers that he identified in earlier studies.

These advances—the model of early-stage disease and the new assay for testing candidate pancreatic cancer biomarkers—are overcoming the two big obstacles that have kept researchers from making headway with identifying biomarkers, Dr. Logsdon said. “These breakthroughs are going to accelerate discovery.”

There are several rationales for starting with preoperative chemotherapy or chemoradiation. “For one, most patients likely have small numbers of metastatic cells that we can’t see on our x-rays,” said Jason B. Fleming, M.D., an associate professor in the Department of Surgical Oncology. “Giving systemic therapy first is a chance to treat those micrometastases.”

A second rationale is that the response to systemic therapy helps clinicians better assess which patients will receive the most benefit from surgery. The decision to perform surgery isn’t taken lightly. Pancreatoduodenectomy, also called the Whipple procedure, is a major operation that involves removal of portions of the pancreas, stomach, duodenum, common bile duct, and gallbladder and then reconstruction of connections between the pancreas, jejunum, common bile duct, and stomach. A typical hospital stay at M. D. Anderson is 11 days, and the recovery period is several weeks. Although the in-hospital death and complication rates are lower at M. D. Anderson than the national average, “the surgery carries significant risk,” Dr. Fleming said. “So our treatment philosophy is to get the most out of the operation that we can, and our recent studies suggest that patients who receive preoperative therapy followed by surgery benefit more than when the surgery is performed first.”

A third rationale for giving preoperative therapy—specifically, chemoradiation—is that the rate of positive resection margins may be reduced. The local recurrence rate for pancreatic cancer after surgery has been as high as 50%. One reason for this high rate is that it’s hard for the surgeon to remove all the tumor cells close to the major blood vessels. Radiation therapy may help kill (Continued on page 4)
those tumor cells before the surgeon even goes in. “In our experience so far,” Dr. Fleming said, “the local recurrence rate is much lower—11%–25% in our recent reports—when chemoradiation precedes surgery.” A randomized trial to confirm these initial findings will start soon.

Doing surgery after preoperative chemotherapy or chemoradiation has another advantage for investigators. “The nice thing about this approach,” Dr. Fleming noted, “is when you take the tumor out in the end, you can look at it and see how well the systemic therapy performed. You can also study the resistant cells that survived all that treatment.”

Systemic therapy: looking for the right combination

Unfortunately, many resistant cells do survive existing systemic therapies for pancreatic cancer, including the standard agent, gemcitabine. This resistance is the reason that inoperable disease has had such a poor prognosis: patients with locally advanced pancreatic cancers have a median overall survival duration of about 12 months from the time of initial diagnosis; those with metastatic disease, only about 6 months. Use of gemcitabine has not prolonged survival durations substantially but has been helpful with palliation of disease symptoms.

To try to improve survival in patients with advanced disease, M. D. Anderson researchers are testing a range of chemotherapeutic and biologic agents, often in combination with gemcitabine, in hopes of finding synergistic anticancer mechanisms. For example, a phase II trial now under way for patients with resectable disease combines gemcitabine and erlotinib (Tarceva) with or without radiation as preoperative therapy. These agents attack tumor cells in different ways. Gemcitabine disrupts DNA replication in tumor cells and sensitizes them to radiation. Erlotinib inhibits epidermal growth factor receptor, a cell-surface protein that signals cells to divide and is overexpressed in many cancers, including those of the pancreas. In another trial, designed for patients with locally advanced disease, erlotinib is being combined with bevacizumab (Avastin), which inhibits tumor angiogenesis; capecitabine (Xeloda), which inhibits DNA synthesis; and radiation therapy. Other mechanisms being evaluated in current clinical trials are prevention of DNA repair (with BSI-201) and inhibition of cell division (with everolimus). Each of these agents has shown promise in preclinical studies or in patients with tumors at other sites.

Countering chemoresistance

The key to success in pancreatic cancer may be combining anticancer drugs with agents that reverse chemoresistance. The phenomenon of chemoresistance is of central interest to M. D. Anderson researchers Gary E. Gallick, Ph.D., and Craig Logsdon, Ph.D., professors in the Department of Cancer Biology, and David J. McConkey, Ph.D., professor in the departments of Cancer Biology and Urology. The three meet weekly to compare notes. “You can kill some pancreatic cancer cells with standard chemotherapy, but most you can’t,” Dr. Logsdon said. “Why is one cell resistant and another one not? That’s the question we want to answer.”

In searching for the mechanisms involved, through gene expression profiles and molecular biology studies, M. D. Anderson researchers have obtained results that suggest that gemcitabine chemoresistance is characterized by a predictable pattern of changes. For example, “one of the striking things that appears to happen is that some of the tumor cells undergo epithelial-mesenchymal transition (EMT),” Dr. Gallick said. “And one of the properties of mesenchymal cells is they are much more migratory, much more invasive”—a property essential to a tumor cell becoming metastatic. In addition, this property is associated not only with resistance to gemcitabine but also with resistance to many other agents.

“We’re trying to be very translational, to take applications from the laboratory to the clinic.”

— Dr. James Abbruzzese
This new understanding of the nature of resistance has prompted several new approaches to treatment. “We think we will be able to reverse the resistance phenotype and sensitize the cells,” Dr. Gallick said. “That’s where I think things are going to go. That’s why we’re excited.”

One treatment approach being tested involves targeting substances involved in EMT. Dr. Gallick’s lab has been studying c-Met, a growth factor receptor that is overexpressed in pancreatic tumors. c-Met levels are increased in cells that have undergone EMT. Dr. McConkey’s lab has been studying the histone deacetylase (HDAC) class of cellular enzymes, which appear to be involved in EMT and gemcitabine resistance. Lab studies involving inhibition of c-Met and HDACs in cancer cells have now led to clinical trials. The c-Met inhibitor XL184 and the HDAC inhibitor suberoylanilide hydroxamic acid (vorinostat) are being tested in ongoing and upcoming clinical trials at M. D. Anderson.

With both c-Met and HDAC inhibitors, investigators hope that EMT can be undone—that the transformed mesenchymal cells will revert to the epithelial phenotype and thereby become sensitive to gemcitabine and other agents. This work addressing reversal of chemoresistance and the potential benefits to patients with pancreatic cancer is still hypothetical, Dr. McConkey said. However, “the good news is we have a lot of excellent models, we have good collaborations in place, and we do expect to get some answers quickly. We think we’re really onto something here.”

In most cases, the diverse projects in progress at M. D. Anderson’s lab have clinical components, Dr. Abbruzzese said. “We’re trying to be very translational, to take applications from the laboratory to the clinic.” With active research on so many fronts and the clinical gains already seen, it seems only a matter of time before pancreatic cancer’s prognosis improves.

For more information, call Dr. Abbruzzese at 713-792-2828.

---

**Clinical Trials in Pancreatic Cancer**

Screening for Early Pancreatic Neoplasia in High-Risk Individuals: The Lustgarten Foundation—NCI SPORE Cancer of the Pancreas Screening Study (CAPS 3) (2007-0193). Principal investigator (PI): Jeffrey H. Lee, M.D. The goal of this clinical trial is to see if pancreatic cancer can be found before any signs or symptoms of the disease appear.

A Randomized Phase II Study of Preoperative Chemotherapy (Gemcitabine and Erlotinib) with or without Radiation Therapy for Patients with Resectable Adenocarcinoma of the Pancreas (2008-0459). PI: Jason B. Fleming, M.D. The goal of this clinical trial is to see if giving gemcitabine and erlotinib with or without radiation therapy before surgery can help to control pancreatic cancer. The safety of this treatment will also be studied.

Phase II Trial of Induction Cetuximab, Gemcitabine, and Oxaliplatin, Followed by Radiotherapy with Concurrent Capecitabine and Cetuximab, Followed by Maintenance Cetuximab and Gemcitabine for Patients with Locally Advanced Pancreatic Cancer (2004-0983). PI: Christopher Crane, M.D. The goal of this clinical trial is to learn if cetuximab combined with chemotherapy (gemcitabine and oxaliplatin) followed by radiation therapy given with chemotherapy (capecitabine) and cetuximab will help to control pancreatic cancer. The safety of this combination treatment will also be studied.

Phase I Trial of Preoperative Radiotherapy with Concurrent Bevacizumab, Erlotinib, and Capecitabine for Locally Advanced Pancreatic Cancer (2007-0044). PI: Sunil Krishnan, M.D. The goal of this clinical trial is to find the highest tolerable dose of capecitabine, erlotinib hydrochloride, and bevacizumab that can be given in combination with radiation to patients with advanced pancreatic cancer.

A Randomized Phase II Study of Gemcitabine plus Erlotinib plus MK-0646, Gemcitabine plus MK-0646, and Gemcitabine plus Erlotinib for Patients with Advanced Pancreatic Cancer (2007-0910). PI: Milind Javle, M.D. The goal of this clinical trial is to find the highest tolerable dose of MK-0646 when given in combination with gemcitabine or gemcitabine and erlotinib for advanced cancer of the pancreas. Another goal is to learn if different combinations of MK-0646, gemcitabine, and erlotinib can help to control advanced pancreatic cancer. (Currently pending activation.)

Phase II Study of Erlotinib and RAD001 (Everolimus) in Patients with Previously Treated Advanced Pancreatic Cancer (2007-0666). PI: Milind Javle, M.D. The goal of this clinical trial is to learn if the combination of RAD001 and erlotinib can slow the growth of advanced pancreatic cancer. The safety of this drug combination will also be studied.

A Phase IB, Open-Label, Dose Escalation Study Evaluating the Safety of BSI-201 in Combination with Chemotherapeutic Regimens in Subjects with Advanced Solid Tumors (2008-0194). PI: David Fogelman, M.D. The goal of this clinical trial is to learn if and how pancreatic cancer may be affected by BSI-201 in combination with gemcitabine hydrochloride. The safety of this combination will also be studied. (Currently pending activation.)

For more information on these and other trials at M. D. Anderson, visit www.clinicaltrials.org.
Modern imaging tests that detect disease or injury inside the body play a vital role in accurate diagnosis and effective treatment. Imaging technology allows physicians to “see” inside organs, bones, and other tissues. In cancer care, doctors use imaging to determine a tumor’s exact size and location and even to reveal how well a treatment is working.

A variety of imaging tests are available, each using a different process. These are the imaging techniques most frequently used in diagnosing cancer.

**X-ray imaging** is the most common way physicians make pictures of the inside of the body. X-rays are a form of radiation, and the images they produce result from differences in how much radiation different tissues absorb. The film or digital recording of these images is called a radiograph.

By studying the radiograph, a radiologist can identify abnormal areas that might indicate the presence of cancer. Mammograms, for instance, use x-rays to look for tumors or suspicious areas in the breast, while chest radiographs help doctors determine whether there is cancer in the lungs or other areas in the chest.

**Computed tomography** (also called CT or CAT scanning) uses x-rays to create detailed images of the body’s interior. For some CT scans, the patient receives a drink or injection of a contrast agent during the exam, which can help highlight specific areas of the internal anatomy. Because the scan information is collected using multiple detectors and a computer system rather than a flat piece of film or digital detector, CT scans produce cross-sectional images, as if the body had been sliced into sections. This yields more detailed information than a standard 2-dimensional radiograph and allows physicians to see tumors or other lesions much more clearly. With CT, for instance, a doctor can tell exactly how deep a tumor is in the body.

**Magnetic resonance imaging** (or MRI) uses radio waves in a powerful magnetic field to create detailed computer images of a patient’s soft tissues, blood vessels, and major organs. Because the image characteristics depend on many different properties, MRI offers better views of soft tissues than CT and can produce images at any angle without the patient being moved. Another advantage is that unlike CT, MRI does not expose the patient to radiation.

For the best results, patients must lie completely still during MRI procedures, which usually last 40 minutes to an hour. Depending on what part of the body is examined, patients may be injected with a contrast agent.

**Positron emission tomography** (or PET) is a type of nuclear imaging that can help identify cancers early and track their response to treatment. Unlike other imaging techniques that show only structures in the body, PET detects areas of increased cell activity and uses the information to create images of those areas.

For the most common PET study, an ¹⁸FDG-PET scan, a patient receives an injection of a safe, radioactive sugar solution about an hour before the scan. Because cancer cells absorb more of this solution than do most healthy tissues, it will accumulate where an active tumor is present. The PET scan “sees” the radiation and shows the radiologist where the sugar solution has accumulated. The procedure usually takes 45 minutes to an hour. PET is sometimes paired with CT, allowing doctors to pinpoint cancer activity on a detailed image of the patient’s anatomy.

**Ultrasonography** (or ultrasound) uses high-frequency sound waves to create images of internal organs, body structures, and blood flow. In this test, a gel is applied to the patient’s skin, and a small hand-held instrument called a transducer is passed over that part of the body. The transducer emits sound waves that can’t be heard by humans. These waves bounce off internal organs and return to the transducer. A computer converts the reflected sound waves (or echoes) into an electronic picture.

Ultrasonography is often used to determine whether a suspicious lump is a solid tumor or a benign, fluid-filled cyst and to guide doctors during biopsies and some types of cancer treatment.

For more information, talk to your physician, or
- visit www.mdanderson.org/departments/radiology
- call askMDAnderson at 1-877-632-6789

OncoLog, October 2008
K. Stueck
©2008 The University of Texas M. D. Anderson Cancer Center
**Delivering “The Guardian of the Genome”**

Success of p53 gene therapy points to a new way of treating cancer

By Joe Munch

Conventional cancer therapies are most effective before a cancer has reached an advanced stage. Surgery and radiation therapy can often treat initial, localized tumors but are less appropriate for recurrent disease. And chemotherapy, while it may kill advanced cancer cells, can also damage normal tissues—with potentially deadly side effects.

However, the results of a recently completed phase III trial of a gene therapy initially developed at M. D. Anderson may point to a new way of treating some relapsed or refractory cancers. The experimental agent Advexin uses a genetically modified adenovirus armed with a gene that kills cancer cells without harming normal cells.

Advexin, which expresses the tumor-suppressing p53 gene, is the first gene therapy to succeed in a U.S. phase III clinical trial for cancer. Jack A. Roth, M.D., a professor in the Department of Thoracic and Cardiovascular Surgery, invented the therapy and co-founded Introgen Therapeutics, Inc., the company that makes Advexin.

“The p53 protein,” Dr. Roth said, “is called ‘the guardian of the genome’ because it protects against damage to the cell. We are all constantly exposed to agents such as sunlight or tobacco smoke that can cause gene mutations. When the gene is functioning normally, p53 can actually help facilitate repair of those mutations or eliminate the damaged cell.”

In most cancers, however, p53 is defective. The thinking behind the Advexin protocol was to take a normal p53 gene and put it into p53-defective tumor cells to cause apoptosis—death—of the cancer cells but not of normal cells. According to Dr. Roth, “When the p53-expression adenovirus is injected directly into tumors, it causes the tumors to shrink or to stop growing. And in a few cases, there are very dramatic responses where the tumors disappear completely.”

Positive results

Introgen undertook the phase III, open-label clinical trial of Advexin at the behest of the U.S. Food and Drug Administration to confirm the results of earlier phase I and II studies of the therapy. (The results of the phase III study were presented to the American Society of Gene Therapy in May and have not yet been published in a peer-reviewed journal.) A group of 123 patients with recurrent squamous cell carcinoma of the head and neck refractory to platinum- or taxane-based chemotherapy was randomly assigned to receive intratumoral injections of Advexin or intravenous methotrexate (an antimitabolite commonly used to treat squamous cell carcinoma) every 3 weeks.

One of the benefits of Advexin, the study showed, was that it is extremely safe: less than 1% of the patients treated with Advexin experienced harmful side effects, whereas 20%–30% of the patients treated with methotrexate had severe side effects such as bone marrow depression and infections; in fact, one patient died from the methotrexate treatment. But the study’s most important finding, Dr. Roth said, was that it was possible to use the p53 protein as a biomarker to predict which patients’ tumors would be responsive to p53 therapy and which would be responsive to methotrexate but not p53 therapy.

“Patients who had favorable p53 profiles—that is, patients with normal p53 protein levels or low levels of mutant p53 protein—had a significant improvement in their survival,” Dr. Roth said. “Overall survival duration, not just tumor response or time to progression, was more than twice as long as that in patients with the unfavorable p53 profile. This is the first randomized clinical trial to show gene therapy is an effective treatment. Most importantly, the p53 biomarker profiles predict which patients will benefit from p53 gene therapy.”

Addressing limitations

According to Dr. Roth, Advexin can be used to treat patients with

(Continued on page 8)
**“Guardian of the Genome” (Continued from page 7)**

extremely advanced disease that is usually not curable—for example, recurrent, refractory squamous cell carcinoma of the head and neck. However, Advexin must be injected directly into a tumor and thus would be ineffective in treating metastatic disease. “Most patients die from systemic metastases that involve multiple organ systems,” Dr. Roth said. “Gene delivery technology is being developed now that can potentially treat metastases.”

One such technique is using nanoparticles to deliver p53. Nanoparticles are artificial constructs that are a little bigger than DNA or a large molecule like hemoglobin but still much smaller than cells. They can be engineered to deliver drugs or genes to cancer cells but not normal cells. Once inside a tumor cell, nanoparticles release their payload. And because they can be given systemically, nanoparticles eliminate the need for injections directly into tumors. Currently, M. D. Anderson researchers are developing nanoparticles that contain p53 and FUS1, another tumor-suppressing gene, to treat non–small cell lung cancer.

**Future applications**

Hundreds of gene therapy trials are currently under way around the world, and according to Dr. Roth, future gene therapies will likely be used concurrently or alternately with chemotherapy or radiation therapy to stimulate immune responses to cancer or as neoadjuvant therapy to prevent tumors from recurring locally after surgery. Eventually, specific gene therapies may be tailored to individual patients’ needs.

“I think the basic concept of delivering genes to cancer cells has great potential,” Dr. Roth said. “Every month, we’re identifying more genes that play a role in the progression of cancer, and these genes could potentially be used as drugs if we have an efficient, effective way of delivering them.”

For more information, contact Dr. Roth at 713-792-7664. Dr. Roth is a shareholder in and paid consultant to Introgen Therapeutics, Inc. The University of Texas System, which includes M. D. Anderson, is also a shareholder in Introgen.

---

When the p53-expressing adenovirus is injected directly into tumors, it causes the tumors to shrink or to stop growing. And in a few cases, there are very dramatic responses.”

– Dr. Jack Roth