“Too often, we researchers are in our own silos. If you look at any major cancer center, they are so subspecialized that the people treating breast cancer might be on one campus, and the people treating gastrointestinal, lung, or head and neck cancer are on another or certainly in another building or clinic. When you’re this spread out, tools to help us pool our research are necessary.”

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New Approaches Tackle Rising Pancreatic Cancer Rates

By Vicki Brower

Taking the immunomodulator simtuzumab with gemcitabine did not statistically significantly increase progression-free survival in advanced pancreatic cancer, according to a phase II study. Simtuzumab’s maker, Gilead Sciences (Foster City, Calif.), reported results of the double-blind randomized trial of 236 patients in September.

Stromal targeting is one of several new approaches to treating this cancer. Gilead designed simtuzumab to target pancreatic cancer’s thick fibrotic stroma, which may shield the tumor from drugs. Another approach uses hyaluronidase to degrade the extracellular matrix, making tumor tissue more permeable for drug absorption. A proof-of-principle trial is testing that enzyme, said Peter Allen, M.D., professor of surgery and associate director of the David M. Rubenstein Center for Pancreatic Cancer Research at New York’s Memorial Sloan–Kettering Cancer Center. Preclinical research with nab-paclitaxel (albumin-bound paclitaxel; brand name, Abraxane) found modest survival improvements possibly due to its ability, alone or with gemcitabine, to reduce tumors’ stromal content.

“Efforts to degrade tumor stroma in pancreatic cancer have been a rocky road, with some drug combinations causing blood clots,” said Robert Vonderheide, M.D., Ph.D., professor of medicine at the Abramson Cancer Center at the University of Pennsylvania in Philadelphia. A study using another form of hyaluronidase plus chemotherapy had stopped because of side effects, said Ramesh Ramanathan, M.D., program lead in gastrointestinal oncology at the Mayo Clinic in Scottsdale, Ariz. As of mid-September, the trial had resumed with safety changes.

Although survival rates for breast, prostate, and colorectal cancers have increased, pancreatic cancer could go from the fifth- to the second-leading cause of cancer-related death in the U.S. by 2030, right behind lung cancer (Cancer Research, May 19, 2014, online). For 30 years, pancreatic cancer has had a 5-year survival rate of 2%. The disease affects only 46,420 U.S. patients per year, but it kills 39,590. The median survival rate after diagnosis has been, until recently, only 5–6 months. According to Steven Hochwald, M.D., vice chair of surgical oncology at the Roswell Park Cancer Institute in Buffalo, N.Y., pancreatic cancer challenges researchers in several ways:

• It is immunosuppressed, which has until recently rendered immunotherapy ineffective.

Moreover, symptoms often occur only in late-stage disease, making early detection and treatment that much harder. For these reasons pancreatic cancer research has received less funding, but that is changing. Private and public research funding is increasing, and pancreatic cancer has a higher profile. Memorial Sloan–Kettering opened the Rubenstein Center in winter 2014. Columbia University, also in New York, opened dedicated translational research and treatment centers. And several new foundations, such as the Lustgarten Foundation and the Pancreatic Cancer Action Network, raise and distribute substantial research funds.

“Over the past 5 years, our understanding of pancreatic cancer has surged. With rising rates of the risk factors of obesity and diabetes and an aging population, if we don’t address it head-on we will be facing an epidemic.”

Robert Vonderheide, M.D., Ph.D.
Scientists are refining treatments and achieving longer survival times. Improved animal models aid research. Researchers are testing new biomarkers to facilitate early detection and better treatments.

A new study (Nature Medicine, October 6, 2014, online) indicates that an increase of certain blood metabolites, branched chain amino acids, may indicate a two-fold higher risk of later developing pancreatic cancer. These same metabolites have been associated with obesity and insulin resistance. Its developer, Brian Wolpin, M.D., a medical oncologist at Dana-Farber Cancer Institute in Boston, Mass. believes that used together with other risk factors such as smoking and inherited genetic variants, this marker could help stratify risk. And clinical trial results with new and existing drugs offer hope that in the next decade pancreatic cancer could be become chronic rather than lethal.

Near-Term Approaches

Between the advent of gemcitabine in 1996, the emergence of nab-paclitaxel and FOLFIRINOX (leucovorin, 5-fluorouracil [5-FU], irinotecan and oxaliplatin), and the new gemcitabine-nab-paclitaxel regimen, survival has improved, with a small number of patients having a 2-year survival, Ramanathan said. (see box). FOLFIRINOX works mostly by damaging DNA, and nab-paclitaxel seems to work by weakening the stroma and damaging DNA, Ramanathan said. More than 90% of pancreatic tumors have KRAS mutations. However, these mutations occur early in disease development, and efforts to target KRAS directly with farnesyltransferase inhibitors and other agents have so far failed. Researchers need new approaches. “In particular, understanding the genome of the pancreatic tumor may provide insights for treatment,” Ramanathan said.

Investigators including David Kelsen, M.D., Eileen O’Reilly, M.D., and Maeve Lowery, M.D., at Memorial Sloan-Kettering Cancer Center observed that BRCA1 and BRCA2 mutations increase risk of pancreatic cancer in some patients (The Oncologist, September 20, 2011, online). They hypothesized that these cancers might be susceptible, as are breast and ovarian cancers with BRCA1/2 mutations, to PARP [poly (ADP−ribose) polymerase] inhibitors and platinum-based chemotherapies. Eileen O’Reilly, M.D. is the principal investigator of a randomized, National Cancer Institute–sponsored international phase II study of gemcitabine and cisplatin with and without the PARP inhibitor veliparib in patients with a BRCA1 or BRCA2 mutation. The group is also performing a phase II single-arm study of veliparib alone in previously treated patients.

Others are investigating focal adhesion kinase (FAK), a tyrosine kinase crucial in cell adhesion and survival signaling. FAK is overactive in pancreatic and other cancers, Hochwald said. Pancreatic cancer also overexpresses insulin-like growth factor receptor 1, which controls growth, differentiation, and development at the cellular and organ levels. This factor also reduces apoptosis in precancerous and cancerous pancreatic cells. Hochwald, who is using nanoparticles to develop small-molecule FAK inhibitors, said that preclinical and cellular studies lead him to believe that targeting both pathways together could work synergistically. Several FAK inhibitors are already in the clinic.

Another approach aims to make pancreatic cancer an operable disease. Using “Cell in a Box” technology developed by Austrianova, in Singapore, this cell therapy delivers ifosfamide locally to the cancer. Ifosfamide has previously shown promise as a chemotherapy against pancreatic cancer, but its effective dose was too toxic to give patients systemically. Instead, in the “Cell in the Box” approach, patients receive one-third of the usual dose of ifosfamide. “Cell in a Box” contains genetically modified cells that express the drug-metabolizing cytochrome P450 and converts the ifosfamide to its active form at the site of the tumor, according to CEO Brian Salmons, Ph.D. A catheter delivers the “Cell in a Box” capsule containing these cells to capillaries feeding the pancreas. This system of local delivery and activation greatly reduces side effects.

The European Medicines Agency fast-tracked this treatment, which is licensed to Nuvilex (Silver Spring, Md.). Nuvilex plans at least two new trials based on earlier phase I/II and phase II trials with a total of 27 patients with advanced pancreatic cancer. In the first, patients received two courses of ifosfamide at one-third the regular dose plus a urological protectant after transplantation of 300 capsules. Median survival after diagnosis rose to 40 weeks, compared with historical control of 28 weeks with gemcitabine, and 1-year survival increased to 36%, compared with 18% for gemcitabine. Four patients also reported improved pain, six were unchanged, and three had slightly more pain (The Lancet, May 19, 2001). However, in a second trial doubling the dosof ifosfamide, patients did not tolerate the drug well. Median survival was only 33 weeks, and 1-year survival was only 23%, suggesting that the lower dose previously used was better (Pharmaceutics, August 15, 2014, online).

“However, nine of the 27 patients were alive after 1 year, and two of these nine patients were alive for 2 years or more,” Salmons said.

An Australian phase IIb trial will test for median survival time and 1-year survival in advanced disease compared with best current treatment, and researchers plan a phase I/II trial for ascites (fluid in the abdomen) in metastatic cancer.

Other trials are evaluating a hedgehog pathway inhibitor, vismodegib, with gemcitabine and nab-paclitaxel in patients with untreated metastatic disease.

Immunotherapy: Beyond Chemotherapy

Immunotherapy enlists the body’s ability to fight cancer, but most researchers had long considered pancreatic cancer unamenable to immunotherapy, owing to an immunosuppressive tumor microenvironment. But Vonderheide and Elizabeth Jaffee, M.D., oncology professor at Baltimore’s Johns Hopkins Sidney Kimmel Cancer Center, recently reestablished tumor immune surveillance by activating macrophages and T cells.

Vonderheide and his collaborator Marina Pasca di Magliano, assistant professor at...
the University of Michigan discovered that one reason for immune suppression in this cancer is the presence of CD4 cells around early tumor lesions. After they eliminated these cells, CD8 cells killed growing tumor cells, keeping the tumor from becoming invasive. Jaffee showed that cyclophosphamide has a similar effect.

Vonderheide also hypothesized that a treatment could harness the CD40 signaling pathway to restart immune surveillance. This pathway is part of the tumor necrosis factor receptor family, which regulates cell proliferation and is an important immune regulator. In 2011 he showed that a CD40 agonist antibody reversed immune suppression and drove antitumor T-cell responses, changing the tumor stroma. Tumors regressed in some patients with inoperable disease. Reproducing this treatment in a mouse model, Vonderheide discovered that tumor regression required macrophages, not T cells or gemcitabine. Antigen-presenting cells, which carry the CD40 receptor, activated macrophages that rapidly infiltrated tumors, killed them, and depleted tumor stroma (Science, March 25, 2011).

“Rather than cancer immune surveillance depending on therapy-induced T cells, we found a CD40-dependent mechanism for targeting tumor stroma,” Vonderheide said. Physically breaching the stroma with the correct immunotherapy may not be necessary. Contrary to previous belief, “tumor stroma is highly susceptible to T-cell and macrophage destruction,” he added. Recently, he showed that eliminating CD4+ lymphocytes prevented pancreatic cancer from growing in mice, with implications for early treatment (Cancer Immunology Research, May 2014).

Jaffee is working with tumor vaccines. In 2011 she reported results from a phase II study in 60 patients with resected cancer with GVAX pancreas. That allogeneic vaccine is composed of an irradiated pancreatic cell line engineered to express granulocyte–macrophage colony-stimulating factor, which attracts and stimulates dendritic cells, and 5-FU–based chemoradiation. Patients received the vaccine first 8–10 weeks after surgery, and then chemoradiation. Those who remained disease free received four GVAX treatments a month apart, and then a final booster at 6 months. Median disease-free survival was 17.3 months, and median survival was 24.8 months. Patients tolerated the vaccine well.

“Some chemotherapy is also immunomodulatory,” Vonderheide said. “This is an important area of investigation, learning how to combine chemotherapy and immunotherapies,” he added.

Jaffee next combined an anti–CTLA-4 drug, ipilimumab (Yervoy) with GVAX, a protein that normally helps keep T cells in check. Blocking CTLA-4 strengthens the immune response. Thirty patients with pretreated advanced cancer received either GVAX plus ipilimumab or ipilimumab alone. Median overall survival was 5.7 months, compared with 3.6 months, and 1-year survival was 27%, compared with 7%.

“We are about to test an anti–PD-1 [programmed cell death protein 1] drug in 80 patients with GVAX in patients with advanced disease,” Jaffee said. The anti–PD-1 drug is an immune checkpoint inhibitor.

Another randomized phase II trial treated 90 metastatic pancreatic cancer patients with GVAX, cyclophosphamide, and CRS-207, a vaccine of live-attenuated Listeria monocytogenes that stimulates innate and adaptive immunity. Researchers discussed results at the January 2014 American Society of Clinical Oncology Gastrointestinal Cancers Symposium in San Francisco. Patients received either two doses of cyclophosphamide and GVAX followed by four doses of CRS-207, or six doses of cyclophosphamide and GVAX every 3 weeks. Patients could repeat these therapy courses. After a median follow-up of 7.8 months, median overall survival was 6.1 versus 3.9 months in patients receiving two doses. Those who received three or more doses had median overall survival of 9.7 versus 4.6 months. Jaffee is also developing a second-generation immunotherapy consisting of three drugs: GVAX, an anti–PD-1 drug, and CRS-207.

“This research has pointed us to a new approach for drug development,” Vonderheide said. “We learned that the immunology of the pancreatic cancer is very complex, but also there are more possibilities to exploit. We need to explore the tumor environment further and develop better agents that will help improve treatment effectiveness,” he said.