Researchers Optimistic About Targeted Drugs for Pancreatic Cancer

A number of investigational targeted therapies are being tested in pancreatic cancer in hopes of finding an effective treatment for a disease that has nearly equal incidence and mortality rates and that has few treatment options. At the same time, some researchers warn that proceeding with these various trials—some whose quality should be questioned—without systematically considering the results serves only to hurt the field.

The goal of a number of new trials in pancreatic cancer is to target the stroma—the matrix or supporting tissue of an organ—and its importance in the development, maintenance, and response to therapy of pancreatic ductal adenocarcinomas. Several studies of agents that may target the stroma were discussed at the recent Pancreatic Cancer 2004 conference in San Francisco, sponsored by the Lustgarten Foundation for Pancreatic Cancer Research, the American Association for Cancer Research, and the University of California at San Francisco.

There has been “increasing evidence for about a decade that normal cells from the stroma—including endothelial cells, fibroblasts, and immune or inflammatory cells—are recruited into pancreatic tumors,” said Douglas Hanahan, Ph.D., professor of biochemistry and biophysics at UCSF.

One way to target the stroma is with drugs that inhibit platelet-derived growth factor (PDGF) receptor. “Preclinical data suggest that PDGF inhibitors, such as imatinib, have activity in an orthotopic model of pancreatic adenocarcinoma in combination with chemotherapy,” said Emily K. Bergsland, M.D., assistant clinical professor at UCSF.

Two phase I trials combining imatinib mesylate (Gleevec) with either doxorubicin or gemcitabine (Gemzar) were reported in 2003 at the annual meeting of the American Society of Clinical Oncology. The gemcitabine study was stopped because of excessive toxicity (myelosuppression and fatigue), but accrual into the doxorubicin study—using lower doses—has continued.

Another class of drugs being tested in pancreatic cancer is vascular endothelial growth factor (VEGF) receptor inhibitors. This growth factor is a well-known angiogenesis promoter and also inhibits maturation of dendritic cells, which are part of the immune system, so use of VEGF inhibitors may not only inhibit angiogenesis but also help improve the host’s immune response, Bergsland said.

A different sort of anti-VEGF agent is bevacizumab (Avastin), a recombinant humanized antibody to VEGF, which was approved for marketing in February on the basis of its activity in combination with irinotecan (Camptosar), fluorouracil, and leucovorin in patients with previously untreated metastatic colorectal cancer.

In advanced, unresectable pancreatic cancer, there are encouraging results from a phase II, multicenter study combining bevacizumab with gemcitabine. According to Lee S. Rosen, M.D., director of developmental therapeutics at the John Wayne Cancer Institute Medical Group in Los Angeles, among 52 evaluable patients, 20% had partial responses. However, there was no correlation between pretreatment plasma VEGF levels and response, survival, or progression-free survival.

Cancer and Leukemia Group B has begun a phase III trial comparing gemcitabine and bevacizumab with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer.

Other trials include a randomized phase II study at Fox Chase Cancer Center in Philadelphia that compares docetaxel and bevacizumab treatment with that of bevacizumab as a single agent in previously treated patients with advanced pancreatic cancer.

In addition to VEGF receptor inhibitors, drugs such as cetuximab (Erbitux) that target the epidermal growth factor receptor (EGFR) are under investigation for pancreatic cancer. The EGFR pathway is involved in such carcinogenic cellular processes as invasion/metastasis and angiogenesis.

In a pilot phase II trial of cetuximab and gemcitabine in 41 patients with advanced pancreatic cancer, the median progression-free survival was 3.5 months. This has led to a phase III trial that Philip A. Philip, M.D., Ph.D., professor at the Karmanos Cancer Institute at Wayne State University in Detroit, is running with colleagues in the Southwest Oncology Group that will study the combination of gemcitabine plus cetuximab versus gemcitabine alone.

Results of various trials show no correlation between the intensity of EGFR expression in patients and outcome of the trials, so it is difficult to predict who will respond to treatment, Philip said.

Another investigational agent, erlotinib (Tarceva), inhibits the tyrosine kinase part of the EGFR molecule and is under investigation in combination with gemcitabine in a large phase III trial of patients with locally advanced or metastatic pancreatic cancer. Median survival was 6.4 months, and 1-year survival was 25.6% in the erlotinib-plus-gemcitabine arm, compared with median survival of 5.9 months and 19.7% 1-year survival in the gemcitabine-plus-placebo arm.

There are a few new targeted drugs emerging from the pipeline that pancreatic cancer researchers are keeping an eye on. The agent SU11248 not only targets the receptor tyrosine kinase inhibitor for PDGF and c-kit, but it also inhibits VEGF. On the basis of preclini-
Screening Methods May Offer Early Diagnosis of Pancreatic Cancer

At least 10% of pancreatic cancers occur in people genetically predisposed to develop pancreatic neoplasms, but there has been no way to detect the disease before it became clinically apparent. Now Johns Hopkins University investigators have defined possible screening methods to detect early forms of pancreatic cancer in this population.

The Cancer of the Pancreas Screening 2 (CAPS2) project included people from families in which pancreatic cancer had affected three or more first-degree relatives as well as people with Peutz Jeghers syndrome (PJS), a rare inherited disorder whose features include a high rate of pancreatic cancer. In addition, three nonpancreatic neoplasms were found in the high-risk group: a stage 1 renal cell carcinoma and two ovarian mucinous cystadenomas, all of which were treated surgically.

In nine of the 78 high-risk patients, endoscopic ultrasound revealed cystic masses associated with dilated pancreatic ducts. Goggins reported at the Pancreatic Cancer 2004 meeting in San Francisco. Only three of these masses were also seen on spiral CT interpreted by experienced radiologists, he added. No mass lesions were seen in the healthy control subjects.

Five of the nine patients with cystic masses have undergone surgery. Four—three from pancreatic cancer kindreds and one with PJS—had intraductal papillary mucinous neoplasms (IPMNs). The patient with PJS also had carcinoma in situ. The fifth patient had a pancreatic intraepithelial neoplasia lesion only.

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“We were trying to detect early neoplasia—in other words, IPMNs and [pancreatic intraepithelial neoplasias], as well as asymptomatic small cancers,” Goggins said. “We found more IPMNs than we expected, possibly because familial [pancreatic cancer] evolves through an IPMN stage more frequently than we thought, which is fantastic because we can detect IPMNs, which are curable more readily.”

Marcia Irene Canto, M.D., associate professor of medicine at Johns Hopkins and lead investigator of the study, said she urges the pancreatic cancer community to set up a consortium to confirm these results in a nationwide study.

—Gail McBride