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-
cal data, it is now in trials as a single agent in a number of cancers. Another multitarget drug of interest is PTK787/ZK222584, an oral receptor tyrosine kinase inhibitor for VEGF that also hits PDGF and some other targets. Phase III trials of the drug in patients with advanced colorectal cancer in combination with chemotherapy are under way.

Pancreatic cancer was one of the first diseases tested with matrix metalloproteinase inhibitors (MMPIs), Rosen noted. Matrix metalloproteinases, which are frequently overexpressed in pancreatic cancer, are associated with tumor progression, including angiogenesis, invasion, and metastasis, and they also appear to be associated with poor prognosis, Bergsland said. Yet trials with MMPIs in pancreatic cancer were disappointingly negative.

“But do we really know the targets for each of the MMPIs that were studied?” Bergsland asked. “If the target was inhibited, is it relevant in stage 4 disease, or should the agents be used in earlier stages? Do we really understand the functional significance of using these MMPIs in vivo?”

Trial Designs

How to use these new agents in general is an issue. “Maybe it doesn’t depend on the type of cancer so much as on the molecular or genetic profile and/or site of metastases of the cancer,” Rosen said. “Our data are limited so far.” He suggested that some of the new targeted drugs might even be used in combination with radiation therapy—including radiofrequency ablation or gamma-knife radiation—in locally advanced tumors. Or when used as adjuvants or neoadjuvants, the drugs might render surgical resection a better option.

“…Translational research is not a one-way street from the lab to the clinic,” Philip observed. “When we fail in the clinic we have to go back to the lab, something we don’t do well. We tend to say, ‘Well, MMPIs don’t work’ and move on. But we need basic science expertise to identify targets, design new therapies, and help select the right patients.” And, as is true for most cancers, researchers are still experimenting with the best study design for new targeted agents. “We think if we don’t want to use a drug as an apoptotic or antiproliferative agent, we can use it alone,” Philip said. “That may not be correct. Or we might give them after a cytotoxic drug, trying to maintain a remission—certainly a farfetched idea for pancreatic cancer. Most studies these days are looking at these agents as chemosensitizers. Is that the best way?”

Philip said there should be emphasis on doing proper pilot clinical trials, not just starting a trial “to help your career or because of some doctor’s interest.” He also urges his colleagues to look for

**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.

The study involved 78 high-risk patients and 140 control subjects. Of the high-risk individuals, 72 had more than one first-degree relative with pancreatic cancer and six had PJS, said Michael Goggins, M.D., associate professor of pathology, medicine, and oncology at Johns Hopkins.

Except for one patient with a past history of acute pancreatitis, all high-risk patients had no symptoms involving the pancreas, and control subjects had no personal or family history of pancreatic disease or pancreatic cancer.

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.

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.

“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