Proteins in Blood Reveal Pancreatic Tumors

By Charlie Schmidt

Although patients diagnosed with pancreatic cancer rarely live more than a year, the disease progresses slowly. Pancreatic cancer can take up to two decades to become symptomatic, and for some of that time it’s potentially curable with surgery. Unfortunately, patients generally aren’t diagnosed with asymptomatic disease—which has spurred a long, frustrating effort to identify blood markers that reveal new pancreatic tumors.

The most widely adopted blood marker for pancreatic cancer is carbohydrate antigen 19-9 (CA19-9), which clinicians measure to monitor cancer progression. But the protein’s levels in the blood also rise with other illnesses, including diabetes, chronic pancreatitis, and gastrointestinal cancers. Moreover, 5%–10% of humans can’t produce CA19-9.

Even so, research on using CA19-9 to screen for pancreatic cancer continues. The American Association for Cancer Research held a special conference on pancreatic cancer in New Orleans on May 19. Findings reported there show that combining CA19-9 with three other proteins improves its screening resolution. Blood samples evaluated came from subjects with early-stage tumors, and “that definitely set our investigation apart from other research,” said Ayumo Taguchi, M.D., Ph.D., assistant professor at the University of Texas M. D. Anderson Cancer Center in Houston, who presented the results.

“Most of the literature describes CA19-9 levels from patients with stage III or IV disease,” he said.

The combined protein panel was better than CA19-9 alone at distinguishing people with pancreatic cancer from healthy control subjects, and from individuals with pancreatic cysts or chronic pancreatitis. Matthew Firpo, Ph.D., associate professor of surgery at the University of Utah School of Medicine in Salt Lake City, described the findings as an important step forward. Firpo and colleagues supplied 42 of the 98 cancer-related samples from a pretreatment collection at the University of Utah. Many samples came from people diagnosed incidentally with pancreatic cancer while being imaged for other abdominal problems, he said.

But the study also had shortcomings. Although the panel in general performed better than CA19-9 alone, most reported differences were not statistically significant. The panel also wasn’t accurate enough to adequately minimize false-positive results.

Process of Deduction

Taguchi and colleagues started by identifying 28 marker candidates from the literature, mouse proteomic studies, and blood samples from patients. The researchers narrowed that set to the three markers (none of them identified pending patent review) combined with CA19-9. They then compared the panel’s screening ability with that of CA19-9 alone in pancreatic cancer versus (1) healthy control subjects, (2) chronic pancreatitis, and (3) pancreatic cysts.

“We have to be careful in how we build a screening test because pancreatic cancer is very rare, chronic pancreatitis is very common, and both elevate similar markers, including CA19-9.”

Only one comparison was statistically significant ($P < 0.05$): the difference in negative predictive value (NPV) between the panel and CA19-9 alone for distinguishing cancer patients from healthy control subjects. (NPV here indicated the marker’s ability to determine who did not have pancreatic cancer.) The panel correctly identified who did not have cancer 94% of the time, whereas for CA19-9 alone the NPV was statistically significantly lower, at 83%.

Avoiding Overlap

Taguchi said that the panel’s ability to distinguish cancer from healthy control subjects was the study’s strongest finding. But Teresa Brentnall, M.D., a gastroenterologist at the University of Washington Medical School in Seattle, argued that the more important question is whether the panel can distinguish pancreatic cancer from chronic pancreatitis, which affects roughly 10% of the U.S. population. Differences between the panel and CA19-9 were not statistically significant in this respect, she pointed out, and both the panel and the marker alone allowed for too many false-positive results.

“We have to be careful in how we build a screening test because pancreatic cancer is very rare, chronic pancreatitis is very common, and both elevate similar markers, including CA19-9,” Brentnall said.

Michael Goggins, M.D., associate professor of pathology, medicine, and oncology at Baltimore’s Sydney Kimmel Comprehensive Cancer Center at Johns Hopkins Medicine, said that, with the emotional and financial costs of a positive result, a screening test for pancreatic cancer needs to approach 100% accuracy (or, in technical terms, specificity). Though the disease is rare, many people are considered at high risk. That includes roughly one in every 300 individuals with adult-onset diabetes, according to Brentnall, as well as individuals with pancreatic cysts, BRCA and other predisposing genetic mutations, and a strong family history of pancreatic cancer. A screening test given to millions of people with a specificity of even 99% could yield
thousands of false-positive findings and strain health care resources.

Though reluctant to rule out that a protein biomarker could reveal new pancreatic tumors, Goggins questions whether proteins in general are selective enough to avoid diagnostic overlap with other, noncancerous problems. Such proteins include the initial 28 in the M. D. Anderson study, he said, most of which are elevated under multiple settings. Goggins’s views on biomarker candidates lean more toward circulating tumor DNA snippets in blood, or circulating tumor cells, which he said could be more specific to pancreatic cancer.

However, Firpo maintains that protein-based panels can be continually improved. “Each biomarker is individually a weak classifier, so our goal is to combine them into stronger classifier panels,” he said. “That approach has mathematical validity, and this latest study shows that we’re making progress, even though we’re not there yet.”

According to Taguchi, the next step will be to validate current results and then investigate the panel in prediagnostic blood samples, which will help ensure its predictive value. David Tuveson, M.D., Ph.D., a professor and pancreatic cancer specialist at Cold Spring Harbor Laboratory in New York, and a program chair at the American Association for Cancer Research conference, agrees that’s the right approach.

Emphasizing optimism over pessimism is important, he said. “However, we now need to substantiate the panel on retrospective cases, and perhaps also with a new prospective series from the general population or from patients who are at high risk.”

Sources for this story all agreed that the panel is not ready for the clinic. Screening high-risk individuals is now performed exclusively with imaging, as described in guidelines from the International Cancer of the Pancreas Consortium, published in *Gut* in January 2014.

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## Cell Cycle Inhibitors Make Progress

**By Vicki Brower**

Palbociclib, the first in a new class of drugs to complete phase II testing, doubled progression-free survival (PFS) in women with metastatic estrogen receptor–positive (ER+) and HER2-negative (HER2−) breast cancer when given with standard hormone therapy, compared with hormone therapy alone.

In the 47-patient randomized study, those taking palbociclib and the aromatase inhibitor letrozole had a median PFS of 20.2 months, compared with 10.2 months for those taking letrozole alone. Women taking the combination lived a mean of 4 months longer (37.5 vs. 33.3 months). But increased survival did not reach statistical significance, said Richard Finn, M.D., assistant professor of medicine at the University of California, Los Angeles, at April’s American Association of Cancer Research meeting in San Diego. The Food and Drug Administration designated palbociclib a breakthrough therapy in April 2013.

Palbociclib targets two cell cycle enzymes, cyclin-dependent kinases 4 and 6 (CDK4/6), which normally facilitate cell cycle progression to DNA synthesis. In certain cancers, these enzymes are abnormally activated. Inhibiting CDK4/6 restores normal cell cycle function and stops uncontrolled cell growth.

“As well as increasing PFS, what is encouraging is that the drug does not appear terribly toxic,” said Eric Winer, M.D., director of breast oncology at the Dana–Farber Cancer Institute in Boston, who was not involved with the study. In the trial, known as PALOMA-1, side effects included decreased white cell count in about 75% of patients, which did not increase infection rate. Dose reductions were common, and 13% left the trial because of side effects.

Until recently, development of CDK inhibitors for cancer was a quiet endeavor. Reports on this drug, developed by Pfizer, and on two others by Novartis and Eli Lilly, started garnering attention last fall. New data from the American Association of Cancer Research in April and the American Society of Clinical Oncology meeting in May show that this new drug class is advancing rapidly through the clinic and showing efficacy. Reports show evidence of single-agent efficacy in one drug and synergy of combination treatments in others in which several pathways are targeted simultaneously. As cell cycle inhibitors, all three compounds are cytostatic and cause tumor apoptosis.

But whether CDK4/6 inhibitors can stop cancer from spreading is another question, said Larry Norton, M.D., deputy physician in chief for breast cancer programs at Memorial Sloan–Kettering Cancer Center in New York. If these drugs are effective, even in combination, a substantial market exists because they can be used in multiple cancer types, analysts say.

“Cancer involves abnormal cell development and growth, and migration, or metastasis,” Norton said. “Attaining tumor regression by slowing down cancer cell development does not touch metastasis,” he added. Stopping uncontrolled cell division will probably only modestly improve response rates of tumor regression and PFS. “That may have only a small effect on overall survival,” Norton said.

Cell cycle inhibition does not address the problem of metastasis, and combining CDK4/6 inhibitors with antimetastasis agents will be necessary, Norton said. The PFS endpoint in this and other trials should be replaced by overall survival, which reflects preventing new metastases, he said.

Winer disagrees: “PFS can be a worthwhile endpoint if toxicity is modest and quality of life is maintained. Ultimately, however, we’d like to see an increase in PFS and overall survival,” he said.