AACR Highlights: Promise for Treating Pancreatic Cancer

By Susan Jenks

Pancreatic cancer, one of the deadliest cancers, may lead to new treatments based on biotypes that are common to many cancers, according to Andrew Biankin, MBBS, Ph.D., head of pancreatic research at the Garvan Institute of Medical Research in Sydney.

“In the current system, the assumption is that cancers are more related to the organ of origin,” Biankin said, adding that using cancer biotypes to target shared genetic mutations across cancers could change treatment for this difficult malignancy. Pancreatic cancer is the fourth-leading cause of cancer death in the United States, and the average 5-year survival rate is less than 4%

Biankin, part of a panel session called Advances in Pancreatic Cancer at the American Association for Cancer Research (AACR) annual meeting in Orlando, April 2–6, proposed a pilot study, using sequencing data from the International Genome Consortium, to address the level of evidence required to validate assays in the multimutation approach. His research team is now sequencing 400 tumors taken from patients with advanced disease.

“It’s a work in progress and a publicly funded effort,” said Anirban Maitra, MBBS., professor of pathology and oncology at John Hopkins’ Sol Goldman Pancreatic Cancer Research Center and one of the session’s cochairmen. “The pilot trial would be proof of principle that biotyping can work.”

Instead of taking a one-size-fits-all approach to cancer, Maitra said, researchers would match shared mutations to a particular drug. For example, a genetic error such as Her2 amplification, found in certain breast cancers and in 2%–3% of pancreatic cancers, might allow some pancreatic patients to be candidates for anti-Her2 drugs, such as trastuzumab or lapatinib.

“But, for targeted therapy to work, the target must be present in that cancer cell, even if the percentage of cancers harboring that change is small,” Maitra stressed. “What’s important is that patient selection be done appropriately.” Otherwise, treatments will fail, or benefits will be incremental, he said, as seen in recent studies combining the targeted therapy erlotinib with gemcitabine.

Pancreatic cancer is genetically complex. Scientists have identified four mutated genes so far, which occur in at least half of these cancers, along with many less-frequent mutations. The most prevalent mutation is in the K-ras gene. More than 90% of pancreatic cancers carry this mutation, making it a desirable target for new treatments. So far, researchers have tried using farnesyltransferase inhibitors to suppress the gene, with mixed success. Some experts also believe the gene holds promise for detecting early disease someday, a long-elusive goal because most patients are diagnosed at late stage.

Other highlights from the session include the following: Early results from a study of abraxane (nab-paclitaxel) with gemcitabine have shown encouraging clinical benefit in pancreatic cancers, suggesting that the combination could become the new standard of patient care, said Jordan Berlin, M.D., clinical director of the gastrointestinal oncology program at Vanderbilt Ingram Cancer Center in Nashville, Tenn. In phase III studies, investigators are using nanoparticles to pierce holes in the stroma’s protective fibrous wall, a tactic offering more efficient drug delivery than paclitaxel alone.

• One new drug candidate targets the ATDC gene, which aids pancreatic cancer cell survival by heightening resistance to DNA-damaging drugs and increasing cell proliferation, said Diane Simeone, M.D., director of the Pancreatic Tumor Program at the University of Michigan Comprehensive Cancer Center. “The gene is overexpressed in almost 90% of pancreatic cancers,” she told the audience at AACR. “The question is, does it cooperate with K-ras to promote disease?”

For mice, the answer is yes. Targeted nanovectors silenced ATDC in established tumors in mice, inhibiting tumor growth and rendering the tumors more sensitive to chemotherapy and radiation, she said.

That finding raises the hope that the
same approach might work in treating locally advanced pancreatic cancers in people. However, Simeone warned, this gene is just one of several signaling molecules involved in tumorigenesis, and more effective predictors of therapeutic response are needed, as are ways to better monitor tumors throughout treatment.

- Two reports published in *Nature* in 2010 challenge the natural history of pancreatic cancer, showing that these cancers do not metastasize rapidly, as commonly believed, but grow slowly over several decades, offering an opportunity for early detection. Christine Iacobuzio-Donahue, M.D., Ph.D., an author of one of the articles, reiterated the researchers’ findings that poor survival in this cancer is due not to early metastatic formation but to late diagnosis. Iacobuzio-Donahue, an associate professor of pathology and oncology at Hopkins, said mathematical models used to estimate the timeline for pancreatic cancer progression found that 11.7 years passed before “parental clones,” which lay the groundwork for cancer’s development, formed. Another 6.8 years elapsed before the tumors became genetically able to metastasize and then another 2.5 years to patient death. The investigators based their findings on an ongoing analysis of genetic changes in tumors from seven patients with metastatic disease.

- Researchers are looking to retool existing drugs for off-label use. One such drug, chloroquine, used to prevent and treat malaria, is already poised for clinical trials to treat pancreatic cancers, according to Hopkins’ Maitra. “It so happens with pancreatic cancers, K-ras drives autophagy, where cancer cells essentially cannibalize part of themselves to survive,” Maitra said, adding that in mice, “chloroquine is a big inhibitor of this process and causes tumor regression.” Moreover, he said, “tremendous safety data already exist because half the world uses it.”

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