Pancreatic Cancer: Will Incremental Advances Begin To Make a Difference?

By David C. Holzman

It made no difference whether the pancreatic cancer patients received 5-fluorouracil (5-FU) plus leucovorin or gemcitabine after surgery: Overall survival, progression-free survival, and quality of life were the same, according to the results of the European Study Group for Pancreatic Cancer (ESPAC-3) trial, published in the Sept. 8 Journal of the American Medical Association.

But for clinicians, a more useful interpretation is that 5-FU is just as effective as gemcitabine, the “gold standard,” and much less expensive, said the study’s principal investigator, John P. Neoptolemos, M.D., head of the division of surgery and oncology at the University of Liverpool in the United Kingdom. These results debunked the prevailing wisdom that pancreatic cancer responds strongly only to gemcitabine and that “everything else was not worth the effort,” he said.

More than that, the finding opens the door to new approaches to treating pancreatic cancer, according to Neoptolemos and others. For instance, the two drugs’ different toxicity profiles offer new options for combinations, suggested Margaret Tempero, M.D., a pancreatic cancer expert at the University of California, San Francisco. “There might be reasons one drug or different combinations of drugs would work better in different individuals, and it’s nice to know you’ve got these options to play with,” said Tempero, who was not involved in the trial.

Looking forward from ESPAC-3, some experts speculate that the field will move toward the sort of incremental improvement in survival that began, for instance, in breast cancer and colorectal cancer more than 30 years ago. In the 1970s and early 1980s, metastatic colon cancer patients fared no better than metastatic pancreatic cancer patients do today, said Todd Bauer, M.D., director of the pancreatic cancer research team at the University of Virginia in Charlottesville. Yet now “we can give those [metastatic colon cancer] patients with disease limited to the liver a 50% or better 5-year survival rate.”

Step By Step
The ESPAC-3 trial was a phase III open-label trial in which 1,088 patients with pancreatic ductal adenocarcinoma, in 159 pancreatic cancer centers, were randomized to gemcitabine or 5-FU after surgery. Patients in the gemcitabine arm survived an average of 23.6 months, compared with 23 months in the 5-FU arm. No statistically significant differences in overall survival, progression-free survival, or global quality of life scores occurred between the treatment groups. About 14% in the 5-FU arm versus 7.5% in the gemcitabine arm suffered serious adverse events.

Although neither drug proved superior in this trial, the next step is to combine them, said Neoptolemos. ESPAC-4 is testing whether gemcitabine with capcitabine (oral 5-FU) can improve survival compared to gemcitabine alone.

Publication of ESPAC-3 came just 3 months after another study, which showed a 4-month gain in survival among metastatic patients. Presented at the American Society of Clinical Oncology meeting in Chicago, the PRODIGE 4/ACCORD 11 trial showed that the drug...
cocktail dubbed FOLFIRINOX (5FU–leucovorin, irinotecan, and oxaliplatin) boosted median overall survival among metastatic patients to 11.1 months, compared with 6.8 months for those on gemcitabine. Although this difference may seem small, it “is a signal of improvement that has not previously been observed in metastatic pancreatic cancer,” said Eileen M. O’Reilly, M.D., of Memorial Sloan–Kettering Cancer Center in New York, who wrote an editorial accompanying the ESPAC-3 article in JAMA.

Tempero agreed: A compound that adds a few months of survival for advanced patients could “maybe double or more” the rate of cure in all resectable tumors, bringing it up to nearly half of those resected, she predicted.

The downside of FOLFIRINOX is a series of grade 3 and 4 toxicities, including vomiting and neutropenia. O’Reilly emphasized the need to select patients who would not be excessively vulnerable. “I still think it’s not going to be an easy combination to give early postop, because of nutrition and level of well-being,” she said. Generally, patients need 6–8 weeks to recover from the highly invasive surgery before undergoing adjuvant therapy.

### Biologic Agents

Experts hope that incremental improvements in survival will also come with newer agents. Neoptolemos said that the future for nonresectable cancers lies in combining new biologic agents, “of which there is a long list,” with gemcitabine and capecitabine. He mentioned abraxane, a paclitaxel-based compound, and vandetanib (Zactima), a multi tyrosine kinase inhibitor, in particular. A large phase III trial with vandetanib in medullary thyroid carcinoma patients, reported at the American Society of Clinical Oncology...
meeting earlier this year, showed a strong positive response among tumors with activating ret mutations. Overactivation of the same gene occurs in pancreatic cancer, according to laboratory studies, Neoptolemos said.

Erlotinib (Tarceva), which targets the epidermal growth factor receptor, is also in a phase III trial by the Radiation Therapy Oncology Group (RTOG0848). Patients are being randomized first to receive gemcitabine with or without erlotinib. Those whose cancer does not progress will then be randomized a second time to 5-FU/capcitabine with radiation or to observation.

Other promising targets in pancreatic cancer include IGF-1R, c-met, ron, Her-2, src, MAPK, and MEK, according to Bauer. His lab is implanting patients’ tumors into mice and characterizing the genetic and molecular pathways that drive growth and metastasis of individual tumors. He is also treating the mice with gemcitabine to develop resistant tumors and comparing those to untreated tumors to investigate what genetic alterations have made the treated tumors resistant. “If it’s upregulation of a particular pathway, we add a drug that targets that pathway.”

A telomerase vaccine in development could also be used in pancreatic cancer, according to Neoptolemos. Telomerase boosts cell survival in the face of many genetic mutations, and the telomerase vaccine would target this enzyme, which is overexpressed in pancreatic and other cancer cells. Such a vaccine, originally developed in Norway and now being produced by Seoul-based KAEL-GemVax, is in phase III studies at the Liverpool Cancer Trials Unit, which Neoptolemos directs. The study aims to complete accrual in October 2011, he said.

**Biology Poorly Charted**

If ongoing trials do produce a series of small advances, that would be an important development in pancreatic cancer, for which the prognosis has barely changed in two decades. In the mid-1980s, adjuvant therapy doubled the number of patients with resectable tumors who survived. But still, only about 20% of resectable patients who receive adjuvant therapy—about 5% of all patients—are cured, Tempero said.

One reason for the minimal progress is the poorly charted biology of pancreatic cancer. The pancreas lies deep within the gastrointestinal tract, where it is both difficult and dangerous to access, since accidental cuts and punctures could breach the barriers that normally keep gut bacteria from causing dangerous infections.

Another problem: Good tumor tissue samples are scarce. Those few patients who go to surgery are selected partly for their low tumor burden. That means little tumor is available for research, said Edward Garon, M.D., an associate director of the thoracic oncology program in the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles.

On top of that, pancreatic cancer cells are sparse within tumor mass, which consists mostly of extracellular matrix proteins, infiltrating fibroblasts, and macrophages, according to Bauer. Moreover, digestive enzymes compromise the quality of the malignant cells.

**Radiation Debate**

Meanwhile, radiation, though controversial, is still under study for pancreatic cancer. The first ESPAC trial results, published in 2001 and 2004, showed no benefit to adding radiation to chemotherapy, and the finding caused “a major shift from using chemoradiation in the adjuvant setting,” according to O’Reilly.

Leaving chemoradiation out of future trials would make them far simpler and cheaper to conduct, yielding results more quickly, according to several investigators interviewed for this article. “Radiotherapy requires planning imaging, frequent visits to the oncologist, and a variety of precautions,” Neoptolemos explained.

Yet others say that studies with design flaws have obscured what they see as radiation’s real benefits. And some clinicians, including Bauer and Perry Shen, M.D., at Wake Forest University Baptist Medical Center in Winston-Salem, N.C., continue to use it. Bauer conducted a small study in which half of 16 patients received conventional radiation dosing, while half received accelerated dosing—getting the same amount of radiation in fewer sessions over a shorter period. Among the former, only one patient’s tumor had a grade 3 pathologic response (meaning that more than 90% of the tumor was destroyed). In the accelerated dosing arm, five of eight patients had a grade 3 response. A phase II trial with accelerated dosing is now under way.

The large RTOG 0848 trial includes a chemoradiation arm and it could settle the question, according to Tempero, but results won’t be in for a decade. “If radiation is important, which I doubt, we would need to use it and deal with the complexity,” said Tempero. “If radiation is eliminated, because it adds little to overall survival, we can become more nimble with drug development in the adjuvant setting.”

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