Stromal Depletion Goes on Trial in Pancreatic Cancer

By Ken Garber

For decades, surgeons and pathologists have likened pancreatic tumors to rocks. That’s because a dense, fibrotic mass called the stroma surrounds the cancer cells in the tumor. Such stroma, consisting of connective tissue, fibroblasts, leukocytes, and blood vessels, accompanies most solid tumors, but its extent and compactness are exceptional in pancreatic cancer. And since pancreatic cancer is exceptional also in its deadliness, researchers have wondered whether the stroma is at least partly responsible.

Some recent studies now make that case. They argue for the idea that the stroma is blocking drug penetration and contributing to tumor survival, and that drugs that punch holes in the stromal barrier can be effective. “It’s hard to get drug into a rock,” said Robert Wolff, M.D., an oncologist at the University of Texas M. D. Anderson Cancer Center in Houston. “If you can soften up the rock, you may be able to get a better therapeutic index.”

Skeptics remain, but several combination therapies are now in clinical trials to test this “stromal depletion hypothesis.” And some oncologists, including Wolff, are already giving certain patients a stroma-targeted drug in an off-label indication, outside clinical trials.

Switching Targets

Their willingness to try something unproven is understandable. Pancreatic cancer is the fourth-leading cause of cancer death in the U.S., with a median survival of less than 6 months and a 5-year survival rate less than 4%. The disease has been stubbornly resistant to experimental drug therapies. And although research has linked mutations in several genes to pancreatic cancer, targeting individual gene defects is unlikely to be broadly effective. In 2008 the group led by Bert Vogelstein, M.D., at the Johns Hopkins Medical Institutions in Baltimore, looking at 24 pancreatic cancers, reported an average of 63 different genetic alterations, with individual alterations varying widely among the cancers. “If you can’t find a consistent target, look at the stroma as the tumor’s Achilles’ heel,” concluded Daniel Von Hoff, M.D., of the Translational Genomics Research Institute in Phoenix, at last year’s annual meeting of the American Society of Clinical Oncology.

One promising stromal target is hedgehog signaling. The hedgehog pathway, which studies of fruit fly genetics originally identified in 1980, was first implicated in pancreatic cancer in 2003. For the next 5 years, cancer researchers focused on hedgehog signaling in the pancreatic epithelium and then in cancer stem cells. Meanwhile, a hedgehog inhibitor from Genentech proved effective in early trials for advanced basal cell carcinoma, which is driven by activating mutations in the hedgehog receptor.


Then, in 2008, Genentech’s Fred de Sauvage, Ph.D., reported that, for hedgehog-expressing tumors lacking mutations in that pathway, hedgehog signaling was occurring not in the cancer cells themselves but in the stroma. Contradicting earlier studies, including those in pancreatic cancer, de Sauvage showed that, in mouse xenografts, hedgehog ligand from the cancer cells was activating the pathway in the adjacent stroma.

Direct evidence for the stromal depletion hypothesis followed in 2009, when a group led by David Tuveson, M.D., Ph.D., at Cancer Research UK in Cambridge, reported in Science that a hedgehog inhibitor could deplete stroma and revascularize poorly perfused tumors in a genetically engineered mouse model of pancreatic cancer. Tuveson showed that gemcitabine (Gemzar) concentration in the tumors rose by 60% if preceded by a hedgehog inhibitor, and the combination more than doubled mouse survival compared with gemcitabine alone. “[Tuveson] showed that not only is the stroma important in the context of hedgehog signaling, but that . . . you can actually target this stroma [by] using hedgehog antagonists,” said Anirban Maitra, M.D., a pathologist at Johns Hopkins. Two clinical trials of the Genentech hedgehog inhibitor GDC-0449 in pancreatic cancer are under way, and a third was pending as of late February (see sidebar).

Clinical Validation?

Some researchers consider the stromal depletion hypothesis already clinically validated, at least for albumin-bound paclitaxel (nab-paclitaxel). A suspension of albumin nanoparticles, nab-paclitaxel was originally
developed as a way to deliver paclitaxel without the castor oil derivative Cremophor. The additive makes paclitaxel water soluble but causes hypersensitivity reactions and reduces the amount of drug going to the tumor. Nab-paclitaxel delivered more paclitaxel to the tumor without increasing toxic effects.

The U.S. Food and Drug Administration in 2004 approved nab-paclitaxel (Abraxane) from the company now called Abraxis BioScience for the second-line treatment of metastatic breast cancer. By then, company scientists had discovered an active mechanism: The albumin in nab-paclitaxel binds to albumin receptors in tumor blood vessels and is released into the tumor microenvironment. (See J. Natl. Cancer Inst. 2004; 96:90–1.) The company also reported that the protein SPARC, which is highly expressed in pancreatic cancer and many other tumor types, actively binds the albumin in nab-paclitaxel and further concentrates the drug in the tumor. This effect leads to what Abraxis founder Patrick Soon-Shiong, M.D., now calls “stromal collapse.”

The SPARC connection proved to be nab-paclitaxel’s bridge to the clinic. In 2007 Jeffrey Infante, M.D., then at Johns Hopkins, reported that most pancreatic cancer tumors express SPARC, especially in the stroma, and that positive SPARC expression predicted poor clinical outcome. Knowing that nab-paclitaxel bound SPARC, Von Hoff launched a phase I/II trial of nab-paclitaxel, in combination with gemcitabine, in metastatic pancreatic cancer.

Von Hoff announced trial results at the 2009 American Society of Clinical Oncology annual meeting. A total of 67 patients were treated, all with stage IV (metastatic) disease. Of 58 evaluable patients at the time, 23 achieved a partial response and 22, stable disease. For all patients, the median time for progression-free survival was 6.9 months, and overall survival was 10.3 months. For the 44 patients treated at what turned out to be the best dose of nab-paclitaxel, the median progression-free survival was 7.9 months, and median overall survival hadn’t yet been reached.

By comparison, median overall survival for patients treated with gemcitabine alone is 5.9 months, and combining it with erlotinib (Tarceva) can give 2 more weeks. So the study with nab-paclitaxel provided a hopeful signal. But since there was no control group, it’s impossible to know if the drug accounts for the improvement; patient selection or other biases could be responsible. Von Hoff called it “an unusual good result.” Maitra went further, calling the survival data “phenomenal.” “I don’t think anything like this has been done in the past, and I think most likely going forward this will have to become the standard of care for advanced pancreatic cancer . . . if the data hold up in the pivotal phase III [trial].” That trial, launched in March 2009 in metastatic pancreatic cancer, is enrolling 630 patients. The primary endpoint is survival, with initial trial data collection scheduled for this June.

Stromal Collapse
Abraxis’s phase I/II trial did not directly explain why nab-paclitaxel was effective in pancreatic cancer, but Maitra tackled the mechanism question by using mouse xenografts. His group implanted 11 gemcitabine-resistant human pancreatic cancer tumors directly into mice and treated them with the nab-paclitaxel–gemcitabine combination. Response rates mimicked those in the clinical trial. Measuring intratumoral drug concentration, Maitra and colleague Manuel Hidalgo found 3.7 times more drug in the tumors treated with the combination than in those treated with gemcitabine alone. Microscopic examination of the tumor tissue showed that nab-paclitaxel treatment depleted the stroma, collapsing it and bringing tumor cells closer to each other and to blood vessels.

“Think of pancreatic cancer as a solid American cheese, and what nab-paclitaxel is doing is making it into Swiss cheese,” said Maitra. “Full of holes.” As a result, he said, more gemcitabine reached the cancer cells in the tumor—the same mechanism that Tuveson demonstrated for hedgehog inhibitors in his genetically modified mice.

Together, the Tuveson and Maitra experiments, coupled with the phase I/II clinical data, give the stromal depletion hypothesis credibility. “I’ve come around to the notion that there probably is a barrier function to the stroma,” said James Abbruzzese, M.D., an oncologist at M. D. Anderson.

Skepticism—and Off-Label Use
How much the stroma contributes to drug resistance, though, is controversial. “It probably explains, at best, part of the story,” said Philip A. Philip, M.D., Ph.D., an oncologist at the Karmanos Cancer Institute in Detroit. “Pancreatic cells are not inherently very sensitive to chemotherapy. And therefore I think increasing the perfusion to get more drug delivered to the cells may improve outcome, but it’s not going to be sufficient for us to make a major advance forward in the treatment of the disease.” Although the hypothesis needs to

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**Selected Clinical Trials for Stromal Depletion in Pancreatic Cancer**

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be tested, Philip said, “I personally do not anticipate or expect that we’re going to see a major leap forward with these studies.”

Nevertheless, some oncologists are already giving nab-paclitaxel to pancreatic cancer patients off label, together with gemcitabine. Wolff, for example, has treated two patients with locally advanced cancer this way. Such patients—about 30% of those diagnosed with pancreatic cancer—have stroma-rich hypovascular tumors that can’t be resected because the tumor encases the superior mesenteric artery. Wolff considers such patients better candidates for nab-paclitaxel than those with metastatic disease, since it’s not clear that the stroma is as extensive in metastases as it is in the primary tumor.

Wolff said he recommended the treatment to two of his patients, 39 and 46 years old, both with insurance plans willing to pay for it. “It was a combination of what Tuveson was saying and what Abraxane was doing for Von Hoff,” he said. “You see that and say, ‘What the hell, let’s give it a shot. Makes sense.’”

Both patients experienced shrinkage of their tumors, he said. One is now a candidate for surgical resection. “There seems to be antitumor activity there,” Wolff said. “Provocative, encouraging. I wouldn’t say [nab-paclitaxel] is clearly the reason, but I’ve been impressed.” The drug combination was well tolerated in these patients.

Maitra sees no downside to such off-label use. He tells patients asking him about nab-paclitaxel that if they can find an oncologist who can give this sort of a combination, they should go for it. “But obviously that is not the official recommendation,” he added.

Philip is opposed to doing this. “Unless I have convincing evidence from a phase III trial that a drug adds, let’s say, a couple of months over gemcitabine in an average patient, I’m not going to really commit my patients to receive it,” he said. “If we want to push the field forward, we have to wait for the phase III trial, we have to put patients on that phase III trial or other . . . trials.” No nab-paclitaxel trial yet exists for locally advanced pancreatic cancer, although one is in the planning stage.

Publication later this year of the complete phase II results, along with the Maitra mouse data, will raise nab-paclitaxel’s visibility. But until phase III is complete, no one will know whether it really extends lives. Whatever the outcome, the stroma is likely to remain a target beyond hedgehog inhibitors and nab-paclitaxel. “We should stop calling the stroma a second-class citizen in pancreatic cancer,” said Maitra. “It is at least an equal partner.”

Dr. Von Hoff receives research support from Abraxis Bioscience and from Stand Up to Cancer for clinical trials of nab-paclitaxel and GDC-0449, respectively, as well as two clinical trial grants from Genentech, the maker of GDC-0449. Dr. Abbruzzese will receive compensation from Abraxis for helping to oversee conduct of the phase III trial of nab-paclitaxel and gemcitabine.

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