Shock Therapy for Late-Stage Pancreatic Cancer Gets Closer Look

By Susan Jenks

An experimental therapy that essentially shocks pancreatic cancer cells into dying may substantially improve survival in patients with locally advanced disease, a recent study suggests.

Several investigators, however, called for more clinical trials before adding irreversible electroporation (IRE) to existing treatments for these difficult malignancies.

The study (*Ann. Surg.* 2015;262:486–494) found that patients with stage III pancreatic cancer who received IRE after conventional chemotherapy and radiation nearly doubled median survival to 24.9 months, compared with median survival in historical control subjects. In the multicenter trial, 200 patients were given either IRE alone or in combination with pancreatic surgery for margin enhancement between July 2010 and October 2014.

Irreversible electroporation works by punching nanometer-sized holes in the membranes of cancer cells, causing cellular instability and triggering apoptosis, or programmed cell death. Short, intensive pulses of electric current pass through strategically placed probes, depending on tumor size and location. Although the procedure can be done percutaneously, or laparoscopically, most are done as open surgery, requiring hospitalization afterward.

"IRE allows us to treat a large percentage of stage III patients whose cancers were considered unrespectable in the past," said Robert Martin II, M.D., Ph.D., F.A.C.S., director of the division of surgical oncology at the University of Louisville's School of Medicine in Kentucky, and the study's principal investigator. "It definitely gives patients options they didn't have before."

At the time of diagnosis, some 80% of pancreatic cancers are considered inoperable, owing to extensive vascular involvement or metastatic disease. At least half of these cancers are locally advanced, or stage III, cancers. In 2016, the American Cancer Society estimates that 53,070 new cases of pancreatic cancer will occur in the United States, with 41,780 deaths, for an overall 5-year relative survival rate of about 7%.

Martin, a paid consultant for AngioDynamics, manufacturer of the NanoKnife/IRE delivery system, said the device kills cancer cells while minimizing injury to surrounding noncancerous cells, blood vessels, and other vital structures. In comparison, thermal-based systems, which "cook" cancer cells to kill them, induce coagulation and destroy neighboring venous and arterial systems. "We don't recommend them," Martin said.

The U.S. Food and Drug Administration permitted marketing of the NanoKnife last year for the surgical removal of soft tissues, although it is not yet approved to treat any disease or condition. Insurers still view the technology as investigational and the federal agency issued a warning letter to the Albany, N.Y., manufacturer in 2011 for marketing the device as a treatment without FDA approval—an issue that AngioDynamics reported has since been resolved.

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The *Annals* study found that nearly a third of patients developed cancer recurrence after a median follow-up of 29 months, but few had local recurrence of their disease. "That means the therapy works," Martin said, adding that multiple tumor-laden studies in animals show that IRE destroys tumors. And some patients, he said, are now out 5 years from treatment.

All patients in the study underwent induction chemotherapy before IRE and slightly over half received chemoradiation therapy as well for 5–15 months, depending on the protocol of each participating institution. Those patients found to be free of metastases and without clinically relevant primary tumor progression became potential candidates for the therapy.

Of the 200 patients in the trial, 150 patients with higher venous involvement got IRE alone, whereas the other 50 received IRE plus surgery. The tumors in both groups were similar in size and both groups underwent similar chemotherapy regimens before IRE.

Assessing Survival

At Johns Hopkins University Hospital in Baltimore, Md., IRE has been used selectively in patients with locally advanced pancreatic cancers for more than 3 years, according to Matthew Weiss, M.D., F.A.C.S., a surgical oncologist specializing in pancreatic and liver cancers. Good safety data on the technology exist, he said, while the efficacy remains promising.

Mokenge Malafa, M.D.

"What I tell my patients is we probably won't know the true efficacy for 5 years," Weiss said. But he described IRE as an old technology newly applied to the pancreas that offers "an attractive way of destroying tumors while preserving blood vessels at the same time."

Still, the main question, not yet answered, Weiss and others agreed, is whether people live longer after undergoing IRE or benefit instead from a fundamental change in chemotherapy in recent years. "Surgeries are local therapy, IRE is a local therapy, but chemotherapy is systemic," he said. Even after surgery to remove the tumor, metastatic disease will reappear in almost all such patients, he explained.

Steven Hochwald, M.D., F.A.C.S., chief of gastrointestinal surgery and vice chair at Roswell Park Cancer Institute in Buffalo, N.Y., called the findings of the *Annals* paper slightly encouraging. But what's unclear, he too said, is whether IRE really makes a difference in patient outcomes, especially in local control of tumor, including nodal metastases.

"If IRE truly helps, we can't tell from this study," he said.

Moreover, although about 10 patients at Roswell have been treated with IRE, so far, he said, a fair number of complications occurred, including blood vessel occlusions and pancreatitis—further showing the need for more study.

Mokenge Malafa, M.D., chair and program leader of the department of gastrointestinal oncology at Moffitt Cancer Center in Tampa, Fla., also stressed IRE's uncertain benefit, as Moffitt awaits the establishment of a formal protocol of its own.

"I feel strongly this should not be done outside a rigorous clinical trial environment," Malafa said, citing potential selection bias that even Martin described as a study limitation in the journal article. Patients not only had to be strong enough to be put through surgery, they also had to have stable disease, a decent performance status, and be fit enough to travel to participate.

Many patients might do just as well without IRE, both Malafa and Hochwald suggested, since investigators have no way of knowing yet whether that might be the case. Nor can they measure IRE's direct effect on the tumor.

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Technical expertise

Another issue concerns the number of probes to use and where to place them.

Weiss said he and Martin are developing an article on IRE criteria, which will include measures of quality control. He acknowledged, though, that technical expertise and training remain crucial to IRE's success, requiring "someone who knows anatomy and also understands this technology."

One contraindication: patients with heart arrhythmias, since an electrical current could trigger a fatal event. But Martin said he has been using cardiac gating for about 6 years to protect the heart and bypass that problem.

Meanwhile, as clinical data continue to accumulate, the government lists five studies looking at IRE in advanced pancreatic cancers on its clinical trials website. One of them, a phase I study, involving just 12 patients, is being conducted by Cherif Boutros, M.D., M.Sc., chief of surgical oncology at the University of Maryland's Baltimore Washington Medical Center.

The goal of the study, which will continue to accrue patients over the next year or so, Boutros said, is to assess the feasibility and safety of IRE in this late-stage cancer population. Boutros said he dislikes the term *NanoKnife* because it misleads patients into thinking their tumors will be cut out with a knife instead of with electric energy.

Unlike others who use more surgical approaches immediately, Boutros said, interventional radiologists at the university's medical center do IRE percutaneously under the guidance of computed tomography first, and then they select a few patients for surgery about a month later.

"We found this approach less invasive for the patient, and in our eyes, was needed to assess the safety of IRE in a small-step fashion," Boutros wrote in a follow-up e-mail.

Although he said that he doubts that any one strategy with IRE will fill all patients' needs in the future, he said, the approach may prove most useful when tumors sit too close to vital arterial structures to be operable. In smaller tumors, especially, "a good ablation potentially can be achieved," he said.

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Heterogeneous and Rare: Toward Histology-Specific Treatment of Soft-Tissue Sarcoma

By Anna Azvolinsky

The U.S. Food and Drug Administration approved the first treatment for metastatic liposarcoma, a type of soft-tissue sarcoma (STS), on January 28. The treatment, eribulin mesylate (Halaven), a systemic microtubule inhibitor, is the first to improve survival of the disease, albeit only by about 8 weeks. In October of last year, another chemotherapy, trabectedin (Yondelis), also was approved for metastatic liposarcoma and leiomyosarcoma, another STS. Trabectedin improved progression-free survival (PFS) by 2.8 months. Compared with the control dacarbazine arm, which had a median PFS of 1.5 months, patients treated with trabectedin had a median PFS of 4.2 months (hazard ratio of 0.55; $p < .0001$). Still, trabectedin did not show an improvement in overall survival in the phase III trial that led to the approval (12.4 months in the trabectedin arm compared with 12.9 months in the dacarbazine arm).

Excluding gastrointestinal stromal tumors, the only targeted agent approved for any type of STS is pazopanib (Votrient), approved for nonliposarcoma STS. All other approved therapeutic options, including the two recently approved ones, are systemic chemotherapies.

"The recently approved eribulin really didn't have a much better overall survival benefit than the control arm because it included not only liposarcoma but also leiomyosarcoma patients. In a subset analysis the overall survival is much better for just liposarcoma patients," said Brian Van Tine, M.D., Ph.D., sarcoma program director in the division of medical oncology at Washington University in St. Louis. "This trial underscores that we have more than 75 different diseases we call soft-tissue sarcoma and that we need to start thinking [about them individually]."

The difficulty in identifying targeted therapies for STS is that those cancers is relatively rare: About 10,000 new STS cases will be diagnosed in 2016 according