Gemcitabine-Radiation Tx Thwarts Pancreatic Ca

BY PATRICE WENDLING
Chicago Bureau

ATLANTA — Concurrent full-dose preoperative gemcitabine and radiation result in significant tumor response and acceptable toxicity in patients with resectable pancreatic cancer, according to data from a phase II multicenter trial.

In previous trials, investigators backed off from giving full-dose gemcitabine (Gemzar) with conventional whole-dose radiation because of high toxicity levels. This protocol, whose results are encouraging, was designed instead to deliver high levels of systemic chemotherapy with lower-dose radiation, Mark S. Talamonti, M.D., said at a symposium sponsored by the Society of Surgical Oncology.

The trial accrued 41 pancreatic cancer patients from five institutions. Twenty of the patients had resectable disease, while the rest showed no evidence of metastatic cancer but had unresectable disease.

Patients were treated preoperatively with three cycles of gemcitabine, and radiation was given during the second cycle. Cycles 1 and 3 consisted of 1,000 mg/m^2 of gemcitabine given intravenously on days 1 and 8 of a 21-day cycle. Cycle 2 consisted of the same gemcitabine dose on days 1, 8, and 15 concurrent with a 5-day, 3-week course of radiation (36 Gy in daily fractions of 2.4 Gy). Nineteen of the 20 patients with resectable cancer completed therapy without interruption, and only one patient experienced a grade 3 gastrointestinal toxicity.

Of the 20 patients taken to surgery, 17 (85%) underwent resections, including 16 pancreaticoduodenectomies and 1 distal pancreatectomy. Biopsy of metastases was performed only on the three patients who could not undergo resection. The complication rate was 24%, and there were no operative deaths. About one in four patients needed a vascular resection. This wasn't due to tumor adherence or invasion of the veins, but rather, was related to an "incredible fibrotic reaction" seen in the resected specimens, possibly as an effect of treatment, said Dr. Talamonti of Northwestern University, Chicago.

At 12 months' follow-up, 10 (59%) of the 17 patients who underwent resection were alive with no recurrence, 4 (24%) had distant metastases, and 3 (18%) had died.

Pathology revealed clear margins in 16 (94%) of the 17 patients who underwent surgery, and unresolved lymph nodes in 11 (65%) of the 17. One specimen contained no residual tumor, and three specimens revealed only microscopic foci of residual disease.

What some of the other trials underestimated is the capability of gemcitabine to serve as a radiation sensitizer, Dr. Talamonti noted. "What we tried to do is decrease the amount of radiation, assuming that gemcitabine was not only acting systemically but that it was also a potent radiation sensitizer," he said.

Another advantage of the protocol is that there was no delay in surgery because it was well tolerated and caused no severe debilitation. All 20 patients underwent surgery within 6 weeks after their last gemcitabine infusion, which is comparable with other neoadjuvant trials, he said.

"I think that's a big advantage of this in addition to the response rates," Dr. Talamonti said. He did not present data on the 21 patients with unresectable disease but said they exhibited higher levels of toxicity than patients with resectable disease because they started with a higher tumor load and had a generally lower performance status.

In general, these patients did show significant treatment responses, and some went on to exploratory surgery.

However, at this point it would be an overstatement to say that the protocol is something that can be used to downstage unresectable into resectable disease, Dr. Talamonti said. ■

Chemo Boosts Pancreatic Cancer-Free Survival

BY JANE SALODOF MACNEIL
Southwest Bureau

ORLANDO — Adjuvant therapy with gemcitabine (Gemzar) nearly doubled disease-free survival following surgery for pancreatic cancer in a phase III trial reported at the annual meeting of the American Society of Clinical Oncology.

Peter Neuhaus, M.D., reported that 179 patients given 6 months of gemcitabine chemotherapy went a median of 14.2 months before their disease recurred. In a control group of 177 patients, relapses occurred a median 7.5 months after surgery.

"For me as a surgeon, it is a milestone in the treatment of these patients because we have so long waited for a real improvement," said Dr. Neuhaus of the Charité University Medical School in Berlin.

Earlier, he told reporters at a press briefing that this was the first prospective, randomized, and controlled trial to clearly show that adjuvant chemotherapy will help pancreatic cancer patients after surgery.

"Gemcitabine may become the standard of care for adjuvant treatment of pancreatic cancer," he said during his presentation, predicting that favorable 3-year and 5-year survival rates will be reported with longer follow-up.

The chemotherapy drug is usually given to patients with inoperable, advanced disease. It is the only drug approved by the U.S. Food and Drug Administration for treatment of pancreatic cancer.

The investigators recruited patients with resectable disease at 88 cancer centers in Germany and Austria from July 1998 to December 2004. Participants were randomly assigned to the control or chemotherapy groups 22-24 days after surgery, creating similar cohorts with an average age of 61-62 years and slightly more men than women. In both arms, 86% of patients had stage T3 or T4 disease, and nearly three-quarters were lymph node positive. More than 80% had an R0 resection margin, and the rest were R1, because patients with more residual disease were excluded.

Patients in the adjuvant therapy arm received 1 g/m^2 of gemcitabine on days 1, 8, and 15, every 4 weeks for 6 months. Monitoring included ultrasound every 8 weeks and CT scans at 32 weeks.

Dr. Neuhaus reported that median disease-free survival with gemcitabine therapy was 19.3 months for node-negative patients and 13.1 months for node-positive patients. In the control group, median disease-free survival was 11.2 months for node-negative patients and 7 months for node-positive patients.

"We go one stage up in prognosis for survival of our patients," Dr. Neuhaus said, describing the benefit to node-positive patients as one of the most striking outcomes of the study. Toxicity was low and was less than expected, he added. The most common grade 3 and 4 events with gemcitabine were low white blood cell count (8.4%), low platelet count (2.8%), nausea (4.5%), and diarrhea (2.2%).

In response to a question, Dr. Neuhaus said none of the patients received postoperative radiation, as this treatment is not used in Europe for pancreatic cancer.

Dr. Neuhaus disclosed research funding and other remuneration from Lilly Oncology.

Eileen M. O'Reilly, M.D., called the results "impressive and provocative" in a discussion of the trial. She emphasized that the findings were preliminary, however, and many questions still need to be answered, including how the investigators defined disease-free survival.

As for changing the standard of practice, Dr. O'Reilly of Memorial Sloan-Kettering Cancer Center in New York said, "There is really no globally accepted standard of care for adjuvant treatment of pancreatic cancer. Observation for patients who are fit post op is probably no longer an acceptable standard, though this is controversial." ■

Erlotinib + Gemcitabine = Controversy

Adding the targeted therapy erlotinib (Tarceva) to gemcitabine produced a median survival benefit of less than 1 month for patients with inoperable pancreatic cancer in another trial reported at the meeting.

The study's outcomes were statistically significant, but controversial. Investigator Malcolm J. Moore, M.D., and discussant James L. Abbruzzese, M.D., interpreted the clinical implications in a plenary session.

Patients were enrolled from October 2001 to January 2003 at 140 centers in 17 countries for this National Cancer Institute of Canada trial. Erlotinib was added to gemcitabine because it inhibits the human epidermal growth factor receptor (EGFR), which is overexpressed in pancreatic cancer.

Dr. Moore of Princess Margaret Hospital in Toronto said the trial was the first to show that an EGFR inhibitor can benefit patients with pancreatic cancer. He reported that 285 patients given gemcitabine and erlotinib had a 1-year survival rate of 24% and lived a median of 6.37 months. In contrast, for 284 patients given gemcitabine and placebo, the 1-year survival rate was 17%, with a median survival of 5.91 months.

The combination arm also had better progression-free survival: 3.75 months, compared with 3.55 months for patients who received the placebo. More of the patients given both agents had a tumor response as well: 57.5%, compared with 49.2% of the control group.

"Whatever subset we look at, the hazard ratio is always less than one," said Dr. Moore, who concluded that the combination treatment improved overall survival by 19% (hazard ratio 0.81) and progression-free survival by 24% (hazard ratio 0.76).

Dr. Abbruzzese, chairman of gastrointestinal medical oncology at M.D. Anderson Cancer Center in Houston, noted that the trial had aimed for a 33% increase in median survival, not 8%. "I do not feel these results clearly alter the standard of care for patients with advanced pancreatic cancer," he said, emphasizing that the benefit was less than a month.

Although Dr. Moore said adding erlotinib had no detrimental effects, Dr. Abbruzzese questioned whether the small survival benefits justified exposing patients to any added toxicity. He called for more studies to identify subgroups that would benefit from erlotinib, which causes a skin rash in patients who respond to therapy.

Based on the data so far, Dr. Moore said that erlotinib seemed to be most effective for subgroups of patients who were male, had poor performance status, were younger than 65 years, or had metastatic disease.

The trial's greatest benefits, he suggested, may be to focus oncologists on better understanding molecular responses to therapy, on earlier intervention in pancreatic cancer, and on determining how to identify patients who will benefit from targeted therapy.

Dr. Moore disclosed a consulting relationship with OSI Pharmaceuticals, which applied to the FDA in April for supplemental approval of erlotinib with gemcitabine in advanced pancreatic cancer. Erlotinib was approved in 2004 for use against locally advanced or metastatic non–small cell lung cancer.