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Fatigue: The Forgotten Symptom?

BY HEATHER LINDSEY

A new study shows that few oncologists are following the National Comprehensive Cancer Network guidelines for treating cancer-related fatigue in their patients with advanced disease. Here's the surprising news about the probable reasons. *Page 26*

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PERIODICALS

Pancreatic Cancer: Gemcitabine Plus Nab-Paclitaxel Prolongs Survival in Patients with Metastatic Disease

BY RABIYA S. TUMA, PHD

In addition to prolonged overall survival, patients receiving nab-paclitaxel had a significant increase in progression-free survival, at a median of 5.5 months in the combination arm versus 3.7 months in the monotherapy arm.

SAN FRANCISCO—Patients with metastatic pancreatic cancer now have another option for treatment, researchers reported here at the Gastrointestinal Cancers Symposium. In a Phase III randomized controlled trial, patients treated with nab-paclitaxel plus gemcitabine had a median overall survival of 8.5 months, compared with 6.7 months for patients receiving gemcitabine alone (***Abstract LBA148***).

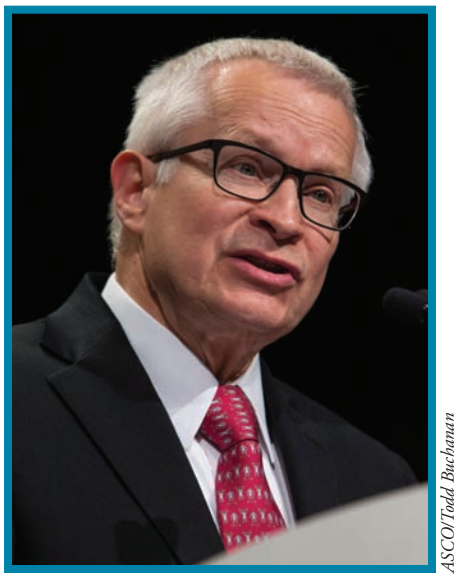
The improvement in survival is statistically significant—with a hazard ratio of 0.72—but that is only part of the story, according to Daniel Von Hoff, MD, Physician in Chief and Director of Translational Research at TGen in Phoenix, Arizona, who led the trial. "You can actually see the patients feel better within a couple of weeks," he said.

In addition to prolonged overall survival, patients in the nab-paclitaxel arm had a significant increase in progression-free survival, at a median of 5.5 months in the combination arm versus 3.7 months in the monotherapy arm. Landmark survival analyses also favored the combination, with the percent difference between the two arms increasing over time: At six months, 67 percent of patients were alive in the combination arm versus 55 percent in the monotherapy arm (22% increase); at 12 months it was 35 vs. 22 percent (59% increase), and at 24 months it was nine vs. four percent (125%).

Post-trial therapy was slightly more common in patients in the gemcitabine-only arm at 9.8 percent, compared with 8.8 percent in the combination-treatment arm.

"Patients with very good performance status—i.e., PS0—have the option of either FOLFIRINOX or nab-paclitaxel plus gemcitabine, whereas those with the lesser PS may be more suited for nab-paclitaxel plus gemcitabine."

Treatment exposure was greater in the experimental arm, with a median treatment duration of 3.9 months compared with 2.7 months. The proportion of doses delivered at full dose was somewhat lower in the combination arm (71% for nab-paclitaxel, 63% for gemcitabine), compared with the monotherapy arm (79%).



ASCO/Todd Buchanan

DANIEL D. VON HOFF, MD: "You can actually see the patients feel better within a couple of weeks."

The data "indicate the very good tolerance of the combination," Von Hoff said during his presentation.

There were an equal number of deaths associated with treatment in the two arms (4% of patients per arm).

Side Effects

The most common grade 3 or 4 hematologic toxicity was neutropenia, at 38 percent in the nap-paclitaxel plus gemcitabine arm and 27 percent in the gemcitabine monotherapy arm, followed by leukopenia (31% vs. 16%), thrombocytopenia (13% vs. 9%) and anemia (13% vs. 12%). Febrile neutropenia was relatively uncommon, affecting just three percent of patients in the experimental arm and one percent in the control arm. Additionally, four percent of patients in each arm died due to treatment-related adverse events.

In terms of non-hematologic toxicities, the most common grade 3 or higher adverse event was fatigue, which affected 17 percent of patients in the experimental arm and seven percent of patients in the control arm. Peripheral neuropathy was 17 percent in the nab-paclitaxel arm compared with less than one percent in the gemcitabine arm. Six percent of patients in the experimental arm had grade 3 or higher diarrhea compared with one percent in the control arm.

With regard to the peripheral neuropathy, Von Hoff emphasized that it is quickly reversible, unlike what occurs with some other taxanes. In particular, in the nab-paclitaxel arm the median time to onset was 140 days, median time to improvement by at least one grade was 21 days, and time to improvement to less than grade 1 neuropathy was 29 days. Additionally, 73 percent of patients affected by peripheral neuropathy were able to restart nab-paclitaxel on study.

Does Not Replace FOLFOXIRI

"Nab-paclitaxel plus gemcitabine is a new standard regimen for patients with metastatic pancreatic cancer," said the Discussant for the study, Philip A. Philip, MD, PhD, Professor of Medicine at Wayne State University School of Medicine and Clinical Professor of Oncology at the Barbara Ann Karmanos Cancer Institute. "But no one is really saying replace FOLFIRINOX by nab-paclitaxel plus gemcitabine."

In fact, during his discussion he noted that an informal comparison of the efficacy and the safety of the two regimens did not obviously favor one regimen or the other: "The comparisons are not as simple as we would like them to be," he said. (Thierry Conroy, MD, and colleagues published the results of the French Phase III trial demonstrating FOLFIRINOX's efficacy and safety in 2011 in the *New England Journal of Medicine* (***2011;364:1817-1825***).

"If we get the tumors to shrink, we have the opportunity to do other things for these patients."

In terms of adverse events, FOLFIRINOX was associated with more fatigue and diarrhea, while there was more neuropathy in patients taking nab-paclitaxel plus gemcitabine. "But keep in mind that the nature of neuropathy is different with the two agents, particularly with regards to reversibility," he said. "Also the proportion of patients who were taken off study drug or refused the study drug in the [nab-paclitaxel plus gemcitabine] trial were not reported."

The efficacy data may favor FOLIRINOX, but that comparison also leads to questions about the two study populations, Philip continued. Whereas the FOLIRINOX trial was conducted at a smaller number of centers (48), all of which were in France, the nab-paclitaxel plus gemcitabine trial enrolled patients from 151 centers in 11 countries. Therefore, the efficacy data may, in part, reflect the different populations, as well as the different regimens.

How to Choose?

When asked how practicing oncologists should choose between the two regimens, he said that both regimens should be

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4 Co-sponsors

The multidisciplinary symposium is co-sponsored by the American Gastroenterological Association Institute, the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology.

Pancreatic Cancer: Adjuvant S-1 'Significantly' Prolongs Overall Survival

BY RABIYA S. TUMA, PHD

"For the first time we now have another option that looks superior to gemcitabine in this setting."

SAN FRANCISCO—Patients treated with S-1 chemotherapy after resection for pancreatic cancer have significantly better overall survival compared with patients who received gemcitabine, researchers reported during a news conference for the Gastrointestinal Cancers Symposium (***Abstract 145***).

In the Phase III randomized controlled trial, two-year overall survival in S-1 treated patients was 70 percent compared with 53 percent for gemcitabine-treated patients, said the lead investigator, Katsuhiko Uesaka, MD, PhD, Medical Deputy Director at the Shizuoka Cancer Center Hospital in Japan.

"S-1 may be considered the new standard treatment for resected pancreatic cancer patients, at least in Japan," he concluded.

When asked whether these data are likely to be transferable to the U.S. patient population, he noted that prior studies indicate that Caucasian patients have different responses to S-1 compared with Asian patients, including a substantially higher rate of diarrhea in Caucasian individuals. For example, he said, that while S-1 is approved for use in Europe for the treatment of gastric cancer, it is used at a lower dose (25 mg/m^2 twice daily for three weeks, followed by one week off) relative to the dose used in the current pancreatic cancer trial (40-60 mg based on body surface twice daily for four weeks, followed by two weeks off).

"If the dose and schedule are optimized, I expect someday it will be applicable for Caucasian patients with pancreatic cancer," Uesaka said.

'Very Impressive, Incredibly Promising'

"The data speak for themselves," said pancreatic cancer specialist Kenneth Yu, MD, Assistant Professor at Memorial Sloan-Kettering Cancer Center. "The results that were presented are very impressive and, I think, will lead to a lot more discussion about whether or not S-1 can be developed in the U.S. population. But certainly these are incredibly promising results."

The trial, called JASPAC 01, enrolled a total of 385 patients who had undergone potentially curative resection for pancreatic cancer. Within 10 weeks of surgery, patients were randomly assigned to receive either gemcitabine (at 1,000 mg/m^2 on days 1, 8, and 15 every four weeks for six courses) or S-1 (four six-week cycles).

The prespecified boundary for the non-inferiority trial was 1.25, with an expected hazard ratio of 0.87. Patients were enrolled between April 2007 and June 2010.

The data safety monitoring board recommended immediate publication of the data given the magnitude of the survival benefit.

Following a preplanned interim analysis in August 2011, the data safety monitoring board recommended immediate publication of the data given the magnitude of the survival benefit. The results are statistically significant for both non-inferiority and superiority, based on a log-rank test.

There were substantial differences in adverse events between the two arms. Patients in the gemcitabine arm experienced more hematologic side effects, whereas patients in the S-1 arm had more gastrointestinal side effects.

The most common grade 3/4 non-GI adverse event was leukopenia, which occurred in about 39 percent of patients in the gemcitabine arm and about nine percent in the S-1 arm, followed by anemia (17% vs. 13%), thrombocytopenia (9% vs. 4%), elevated AST (5% vs. 1%) and elevated ALT (4% vs. 0.5%).

KATSUHIKO UESAKA, MD, PHD: "If the dose and schedule are optimized, I expect someday the results will also be applicable for Caucasian patients."

The most common grade 3/4 GI side effect was diarrhea (0% in the gemcitabine arm vs. about 5% in the S-1 arm) followed by stomatitis (0% vs. 3%), and vomiting (1.0% vs. 2%). Anorexia was more common in the gemcitabine arm than in the experimental arm (about 6% vs. 8.0%); fatigue was more common in the S-1 arm (4.7% vs. 5.4%).

"Pancreatic cancer remains highly lethal worldwide, but one-third of patients can undergo resection with curative intent," said the moderator of the news conference, Neal J. Meropol, MD, Chief of the Division of Hematology and Oncology in the Department of Medicine at University Hospitals Case Medical Center and Case Western Reserve University School of Medicine. "Among these patients, we've viewed gemcitabine as the standard adjuvant therapy to improve survival over surgery alone.

"For the first time we now have another option that looks superior to gemcitabine in this setting—improving the cure rate for pancreatic cancer that is resectable."

→NAB-PACLITAXEL

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considered. "Patients with very good performance status—those with PS0—have the option of either FOLFIRINOX or nab-paclitaxel plus gemcitabine, whereas those with the lesser PS may be more suited for the nab-paclitaxel plus gemcitabine."

The decision will also depend on patient preferences, he added. For example, if patients are particularly concerned about fatigue or do not want to carry an infusion pump for 48 hours every two weeks, they may prefer nab-paclitaxel plus gemcitabine.

At the end of his discussion, Philip emphasized the need for more progress in pancreatic cancer. "Nab-paclitaxel alone with gemcitabine or in combination with other agents must be considered for further development in earlier-stage disease and as a backbone for adding in biologicals," he said.

This trial "is [only] the fourth positive trial in pancreatic cancer in more than four decades. We really need to do better."

For his part, Von Hoff said he thinks this new regimen will help further progress in the field because it stabilizes patients. And that, he told *OT*, is critical for testing other agents and seeing the effect of other agents in these patients. "If we get the tumors to shrink, we have the opportunity to do other things for these patients."

The study was funded by Celgene. Von Hoff has received honoraria and research funding from the company and has served as a paid consultant for the company. His coauthors on the study reported similar information. Philip reports receiving funds or being a consultant for several companies, but did not report any association with Celgene.