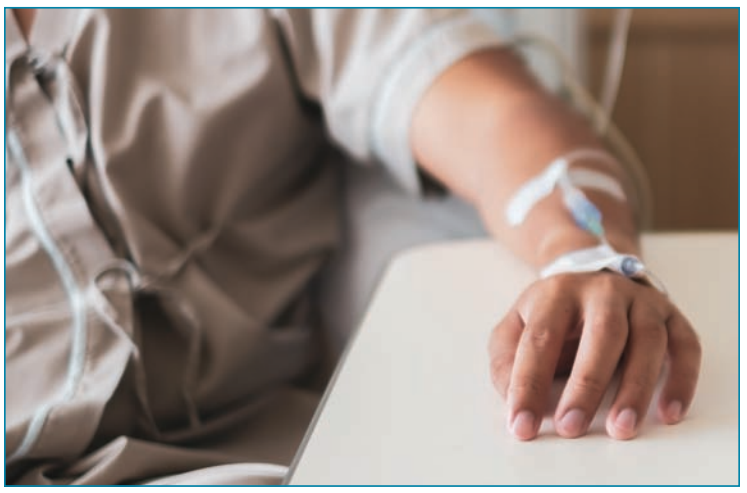
Pre-Surgical Chemotherapy in Early-Stage Pancreatic Cancer

BY AMY GALLAGHER

In the adjuvant treatment of resected pancreatic cancer, combination regimens have shown strength over single agents. However, treating presurgical pancreatic cancer with two frontline combination regimens has yet to be examined systematically. Until now.

The first-of-its-kind randomized clinical trial has delivered a series of successful outcomes for administering presurgical chemotherapy, from two different regimens, to pancreatic cancer patients. While the trial did not result in better survival rates—as compared with data from other pancreatic cancer trials testing chemotherapy after surgery, the study highlighted three positive results as reported by Davendra Sohal, MD, MPH, Co-Chair of the SWOG Cancer Research Network and Associate Professor of Medicine at the University of Cincinnati College of Medicine.



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Sohal and his colleague Syed Ahmad, MD, Chair of the SWOG Surgery Committee, launched the SWOG S1505 trial to compare two common chemotherapy regimens for pancreatic cancer, marking the first trial in the NCI National Clinical Trials Network to test chemotherapy prior to pancreatic cancer surgery. It represented the SWOG's fifth study in 2015, with the S1505 trial completed in 2018.

The experimental and developmental therapeutics administered at early-stage pancreatic cancer were conducted by researchers as a Phase II trial. The research results were first presented at the 2020 American Society of Clinical Oncology Annual Conference.

The two drug combinations had yet to be studied simultaneously in the preoperative setting prior to the S1505 study, which showed the two regimens performed similarly, with a 2-year overall survival (OS) of 47 percent on the mFOLFIRINOX combination, and a 2-year OS of 48 percent on the gemcitabine/nab-paclitaxel combination.

As the first of its kind study, researchers showed that pancreatic cancer patients who elect presurgical chemotherapy can expect a successful surgery without significant postoperative complications. The results proved it is possible to conduct trials that can safely compare chemotherapy treatments administered prior to surgery.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Identify staging criteria and survival rates for patients with pancreatic cancer. 2. Evaluate the patient enrollment, drug regimens used, and results from the Phase 2 S1505 trial.

Disclosure: The author(s), faculty, staff, and planners in any position to control the content of this activity, have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

Improved Treatment for the Future

"While the trial findings did not show a direct patient benefit, the results showed that it is possible to safely administer chemotherapy prior to pancreatic cancer surgery, and it also paved the way for improved treatment testing in the future," Sohal noted.

According to the Pancreatic Cancer Action Network, stage IA, the tumor is confined to the pancreas at 2 cm or less and is resectable; stage IIA-IIB are considered locally advanced, the tumor is greater than 4 cm and extends beyond the pancreas to nearby blood vessels, nearby lymph nodes or a combination, but not another organ or major nearby arteries. The American Cancer Society SEER database reports the 5-year pancreatic cancer survival rates based on groups: localized at 39 percent, regionalized at 13 percent, and distant at 3 percent. Unfortunately, Sohal said about half of his patients arrive at stage IV.

"Technically, some patients with stage I or II are diagnosed in time, but the cancer appears to have already spread beyond the pancreas which makes the outcomes poor," he said. "Even in the early stages, the cancer is probably more advanced than what we can tell by standard tests."

Equivalent Results of Regimen Combinations

For patients in stage I or II, Sohal and Ahmad proposed to test two chemotherapy regimens to determine if one or both of the drug combinations could extend life. The two combinations tested were mFOLFIRINOX, consisting of three chemotherapy drugs—fluorouracil, irinotecan, and oxaliplatin; and the second combination contained gemcitabine and nab-paclitaxel.

"We didn't know which regimen was best, so we studied both to determine the best regimen," said Sohal. Based on overall data, the SWOG trial did not find any differences between the two regimens.

"Both therapy regimens are equivalent, which is an important outcome of the trial," he said. "That was a very important lesson to learn and was quite surprising. Now we know."

In the S1505 trial, 102 eligible early-stage (stage I or II) pancreatic cancer patients were selected on day 1 and enrolled at the time of diagnosis, Sohal explained. Patients were randomly assigned to receive either the mFOLFIRINOX or the gemcitabine combination, both before and after surgery. However, some patients were too sick from presurgical chemotherapy or for other reasons, only 73 of the 102 eligible patients underwent surgery. Of those, 61 started and 48 completed chemotherapy. The average age of the patient cohort was 64 years with 57 percent male patients. The researchers questioned whether or not improved outcomes could be achieved by administering mFOLFIRINOX prior to surgery.

"The results of our research have allowed us to create a clinical trial platform that can be applied to test future presurgical chemotherapy treatments for pancreatic cancer," Sohal stated. "More importantly, the study shows that such a comparison can be conducted safely. Most of the patients who received chemotherapy could continue on successfully with surgery."

In addition, by pre-treating a tumor prior to surgery, the S1505 team opened the door for pre- and post-surgical comparisons of tumor tissue in pancreatic cancer. Molecular testing of tumor tissue could reveal genetic and other cellular changes that might shed important light on the effects of chemotherapy drugs on early-stage pancreatic cancer, he said.

"We also studied tumor specimens removed during surgery, which we tested for detailed tumor makeup of molecular tissue while monitoring the immune environment to see how the body fights the cancer," said Sohal.

Lessons Applied to Future Studies

Sohal said several important lessons emerged through the trial, including the procedural knowledge to conduct a trial with a central review of the scans at stage I and II using two equivalent regimens.

"We learned this is the maximum we can benefit from chemotherapy and now we have to move the needle," he said. "To cure more patients, we need better treatment in addition to chemotherapy, and we are working on drugs that are more promising."

Sohal said the trial confirmed the safety of this approach, as well as the feasibility, making way for future opportunities for improvement. "We are currently working with drug companies and have promising candidates."

"With the outcomes of these important lessons, the most enlightening result was the regimens are safe and feasible; we are not harming patients," said Sohal. "This approach can be adopted now and is adopted at many centers. The results of the trial outcomes have made the regimens acceptable in that patients can be reassured of the safety of this kind of therapy." Surgical outcomes of S1505 were detailed in July 2020 in *Annals of Surgery* (doi: 10.1097/SLA.0000000000004155). OT

Amy Gallagher is a contributing writer.