Multidisciplinary Management of Pancreatic Cancer

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

At JADPRO Live Virtual 2021, presenters reviewed the epidemiology of pancreatic cancer, treatment options for patients with different stages of pancreatic cancer, and the most common symptoms and complications related to pancreatic cancer and their management in a collaborative practice model.

An aggressive disease with a high mortality rate, the 5-year relative survival of pancreatic cancer remains a dismal 10.8%. A multidisciplinary approach with supportive oncology and palliative care expertise continues to offer the best chance for successful care.

During JADPRO Live Virtual 2021, Pelin Cinar, MD, MS, a specialist in gastrointestinal oncology, and Patricia Zendejas, MSN, ANP-C, AOCNP®, a nurse practitioner at the University of California, San Francisco, differentiated the treatment options for patients with different stages of pancreatic cancer and discussed the management of the most common symptoms and complications related to the disease.

BACKGROUND

In 2021, there were an estimated 60,430 new cases and 48,220 deaths due to pancreatic cancer. At only 10.8%, the 5-year relative survival of pancreatic cancer compares unfavorably with other tumor sites. The median age at diagnosis is approximately 70, said Dr. Cinar, but there has been a recent uptick in pancreatic cancer among younger patients.

Risk factors associated with the disease include the following:

- Cigarette smoking
- Heavy alcohol consumption
- Chronic pancreatitis
- Occupational exposure to chemicals (beta-napthylamine and benzidine)
- Low 25-hydroxy vitamin D levels
- Increased BMI
- Diabetes mellitus
- Germline mutation: *CDKN2A* (p16), *BRCA2*, *PALB2*, *STK11* (Peutz-Jeghers), mismatch repair genes (Lynch syndrome).

Pancreatic cancer is generally treated according to the following classifications: resectable disease, borderline resectable disease, locally advanced disease, and metastatic

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disease. The first three classifications depend on the degree of contact that the tumor has with essential blood vessels, which requires a multidisciplinary discussion and input from surgeons.

"Early diagnosis is paramount with pancreatic cancer because patients with resectable disease have the highest chance of cure," said Dr. Cinar. "Unfortunately, approximately 80% of patients have unresectable disease at the time of diagnosis."

The recurrence rate after resection is very high (66% to 92%), and 80% of recurrences occur within 2 years of surgery (Bond-Smith et al., 2012).

NEOADJUVANT THERAPY

According to Dr. Cinar, at this time, there is limited evidence to recommend a specific neoadjuvant regimen. Acceptable neoadjuvant options per National Comprehensive Cancer Network (NCCN) guidelines include the following:

- FOLFIRINOX +/– subsequent chemoradiation
- Gemcitabine + albumin-bound paclitaxel +/– subsequent chemoradiation

"When choosing the optimal treatment option, it's important to consider the patient's performance status so that we can determine which regimen they are able to tolerate and ultimately successfully proceed to surgery," Dr. Cinar said.

Ms. Zendejas underscored the importance of collaborative practice in clinic. Prior to each chemotherapy infusion, for example, patients are evaluated by either the advanced practitioner (AP) or the physician.

"During these visits, the clinician reviews vitals, labs and manages side effects by modification of chemotherapy dosage or symptomatic support," said Ms. Zendejas. "Throughout the patient's care, the physician, AP, and registered nurse are in continuous close communication."

ADJUVANT THERAPY

Like neoadjuvant therapy, there is not a single definitive standard of care for pancreatic cancer in the adjuvant setting. Rather, said Dr. Cinar, treatment needs to be determined on a case-by-case basis and depends on multiple factors.

If no prior neoadjuvant chemotherapy has been offered, preferred regimens in the adjuvant setting include the following:

- Modified FOLFIRINOX (limited to patients with ECOG 0–1)
- Gemcitabine + capecitabine
- Gemcitabine monotherapy (if marginal performance status)
- 5-FU or capecitabine monotherapy (if marginal performance status)
- If prior neoadjuvant chemotherapy was offered, however, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

"We consider chemoradiation in the instance of a positive margin or R1 resection," said Dr. Cinar, who noted that chemotherapy is often followed by chemoradiation. "Capecitabine is the chemotherapy that we use with concurrent chemoradiation for better tolerability, and there may be subsequent chemotherapy."

"If systemic chemotherapy precedes chemoradiation, restaging with imaging should be done after each treatment modality," Dr. Cinar added.

According to Dr. Cinar, adjuvant treatment should be administered to patients who have adequately recovered from surgery and should be initiated within 12 weeks.

Regarding collaborative clinic practice, Ms. Zendejas noted that patients often receive pancreatic enzymes to treat exocrine pancreatic insufficiency and emphasized that the AP and RN should frequently follow up with patients to assess symptoms.

"Although there is somewhat standard dosing to start a patient with pancreatic enzymes, this medication typically requires a lot of dose adjustment to optimize treatment of the symptoms," said Ms. Zendejas. "Referral to a nutritionist is also essential for a lot of these patients."

METASTATIC THERAPY

When deciding on treatment of metastatic disease, Dr. Cinar underscored patient performance status and recommended enrollment in clinical trials, if they are available.

The NCCN preferred regimens for good performance status include:

- FOLFIRINOX
- Gemcitabine + albumin-bound paclitaxel
- Other gemcitabine-based doublets

For patients with poor performance status, the NCCN recommends:

- Gemcitabine monotherapy
- Capecitabine monotherapy
- 5-FU monotherapy

The next question is whether patients benefit from single agent vs. combination chemotherapy. According to Dr. Cinar, data have shown that individuals with good performance status tend to have survival benefit from combination therapy. Conversely, patients with poor performance status (ECOG ≥ 2) do not tend to benefit from combination therapy, so single-agent therapy should be considered in those cases.

These recommendations are based on data from the landmark PRODIGE 4/ACCORD 11 trial, which compared FOLFIRINOX (5-FU, irinotecan, and oxaliplatin) with a backbone gemcitabine monotherapy (Conroy et al., 2011).

Results of the study, which included 15 centers in the phase II setting and 48 centers in the phase III setting, showed that patients who received the combination therapy of FOLFIRINOX had a higher overall survival compared with those patients who received gemcitabine monotherapy (11.1 months vs. 6.8 months). With a median follow-up of 26.6 months, progression-free survival also nearly doubled in the FOLFIRINOX arm vs. gemcitabine monotherapy (6.4 vs. 3.3 months).

In addition, data showed significantly longer periods of improved quality of life for patients receiving FOLFIRINOX compared with gemcitabine. Global health score, physical, cognitive, social functioning, and six symptom domains were included in the quality-of-life measurements.

More recently, the MPACT trial compared gemcitabine plus nab-paclitaxel (albumin-bound paclitaxel) with gemcitabine monotherapy. This combination also showed improved overall survival of 8.5 months compared with 6.7 months in those patients who received gemcitabine monotherapy (Von Hoff et al., 2013). Progression-free survival also improved from 3.7 months to 5.5 months with the combination therapy.

Although a head-to-head comparison of FOLFIRINOX and gemcitabine plus nab-paclitaxel has not been conducted, Dr. Cinar highlighted a few key differences from their respective trials. PRODIGE enrolled more than 50% fewer patients than the MPACT trial, which also included patients with slightly lower performance status.

"The overall survival of the controls arms in both studies was almost identical, but the overall survival on FOLFIRINOX was 11.1 months compared with 8.5 months with gemcitabine plus nab-paclitaxel," said Dr. Cinar. Although, she noted that without a trial with head-to-head comparison, we cannot make conclusions from these differences in overall survival.

GASTRIC OUTLET OBSTRUCTION AND PAIN

Ms. Zendejas reported that between 10% to 25% of patients with metastatic pancreatic cancer present with either a full or partial gastric outlet obstruction, which may be treated with an enteral stent placement. Close monitoring of patients is required following a stent placement, said Ms. Zendejas, and it's important for patients to comply with a low-residue diet.

"A nutritionist will help guide the patient's diet and give them very specific information regarding which foods to avoid," she said. "The AP, registered nurse, and physician should also monitor for any signs and symptoms of a problem with the stent."

According to Ms. Zendejas, early palliative care collaboration is vital for management of symptoms, including pain. The first line of treatment for pain is usually narcotics, she said, but can also include celiac plexus neurolysis for abdominal pain with radiation to the back. For patients with bone metastases, palliative radiation therapy can also be considered (Table 1).

SPECIAL POPULATION: *BRCA* MUTATION

A small subset of patients with pancreatic cancer can also have mutations of the *BRCA1* and/or *BRCA2* gene, which is integral to double-strand DNA repair. Dr. Cinar reported that patients with stage III/IV disease and germline mutation of *BRCA* fair better with platinum-based chemotherapy (22 months vs. 9 months; Golan et al. 2014).

Data from the POLO trial also showed that maintenance olaparib (Lynparza) provided statistically significant improvement in progression-free survival for patients with germline *BRCA*-mu-

Table 1. Symptom Management in Pancreatic Cancer

Gastric outlet obstruction
- 10%–25% of patients
- Esophagogastroduodenoscopy: Malignant stricture at the duodenal sweep with successful enteral stent placement (vs. percutaneous endoscopic gastrostomy vs. gastrojejunostomy+/– J-tube)
- Important to comply with a low-residue diet following enteral stent placement

Pain
- Early palliative care collaboration is vital for management of symptoms, including pain
- Management of pain beyond narcotics can include celiac plexus neurolysis (for abdominal pain with radiation to the back)
- If there are bone metastases, palliative radiation therapy can also be considered.

tated metastatic pancreatic cancer whose disease had not progressed during platinum-based first-line chemotherapy (Golan et al., 2019). According to Dr. Cinar, however, there is currently no overall survival benefit reported, and the study did not address patients with somatic *BRCA* mutations.

"Every patient who has locally advanced disease or metastatic disease with pancreatic cancer should undergo somatic mutation analysis or a next-generation sequencing to determine if there are any targetable or actionable mutations in their tumor," said Dr. Cinar.

Disclosure

Dr. Cinar has acted as a consultant for Astellas. Ms. Zendejas had no conflicts of interest to disclose.

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