How Will I Treat This Patient? – Case Series

First-Line Therapy for Metastatic Pancreatic Cancer: A Case-Based Review of Current Evidence

Patient Presentation and Previous Medical History

A 64-year-old female presented to the local ER with nausea/vomiting and upper abdominal pain. She had noticed increasing fatigue and unintentional weight loss of 15 lbs in the last 3 months. She also reported darkening of urine and itchy skin over the last week. On exam she was noted to be afebrile with mild tachycardia (heart rate 112) but otherwise stable vital signs. She was jaundiced with yellowish discoloration of sclera and skin. Abdominal examination revealed epigastric tenderness and an enlarged liver extending 2 cm below the costal margin. Review of her medical history was significant for medication controlled diabetes mellitus and hypertension. She had a hysterectomy 15 years ago for dysfunctional uterine bleeding. Family history was notable for lung cancer in her father at age 70. She has never smoked and does not use alcohol or other recreational drugs and works as an administrative assistant in a law firm.

Laboratory Tests

Laboratory tests revealed a normal complete blood count and kidney function. Her liver function tests were abnormal with elevated bilirubin at 9 mg/dL and alkaline phosphatase of 883 U/L. CT abdomen revealed multiple hypodense lesions in the liver, largest measuring 2.6 cm, and a 3 X 2.5 cm mass in the pancreatic head. There was also intra- and extrahepatic biliary dilatation with the common bile duct measuring 1.4 cm.

What is the best next step in management?

A. Obtain an ultrasound guided liver biopsy
B. Order an ERCP/EUS for biliary stenting and pancreatic FNA
C. Begin antibiotic therapy for multifocal liver abscess
D. Begin combination chemotherapy for metastatic pancreatic cancer
Using this case as an example, we will review the diagnosis and management of pancreatic cancer. We will also discuss the management of symptoms associated with pancreatic cancer.

Pancreatic cancer is an aggressive and deadly entity with an estimated 49,000 new cases and approximately 40,560 deaths in 2015. [1] It is a disease of older adults with a median age of diagnosis of 71 years. [1] Several environmental factors have been associated with an increased risk of pancreatic cancer, but evidence of a causative role exists only for tobacco use and possibly higher body mass index. [2] The risk of pancreatic cancer in smokers is 2-3 times that in nonsmokers; the risk increases with greater tobacco use and longer exposure to smoke. [3] Some studies have pointed to an increased risk among patients with a history of diabetes or chronic pancreatitis, and less convincingly chronic cirrhosis, and Western diet. [4, 5] Approximately 10% of pancreatic cancer is familial. [6] The risk of pancreatic cancer is 57 times higher in families with four or more affected members than in families with no affected members. [7] The genetic basis for these associations is not always defined, but many are related to germline mutations in genes like BRCA2 and the partner and localizer of BRCA2 PALB2, [8, 9] CDKN2A (familial melanoma syndrome), [10] STK11 (Peutz-Jeghers Syndrome), [11] andMismatch repair genes (Lynch Syndrome). [12]

Presenting symptoms of pancreatic cancer may vary, but most patients have vague abdominal discomfort with radiation to the back, obstructive jaundice, and systemic manifestations such as asthenia, anorexia, and weight loss. Other less common manifestations include deep and superficial venous thrombosis, liver-function abnormalities, abdominal distension, and depression. [2] Tumors arising from the head of pancreas often cause obstructive cholestasis leading to clinical jaundice, as in the case presented. Rarely, due to proximity to the duodenum, a pancreatic head mass can lead to duodenal narrowing (pressure or direct infiltration) presenting as gastric outlet obstruction or gastrointestinal bleeding. Both of these complications can be managed initially by an interventional gastroenterologist and may require biliary or duodenal stent placement. If stent placement is unsuccessful, surgical bypass may be required.

The proximity of pancreatic tumors to the neurovascular bundle can result in infiltration or compression by tumor, leading to pain which radiates to the back. Multi-detector CT, using a dual phase pancreas protocol (pancreatic and portal venous phase) with extension of imaging to include chest and pelvis is the recommended initial staging study for pancreatic cancer. [13] Endoscopic retrograde cholangiopancreatography (ERCP) combined and endoscopic ultrasound (EUS) are also typically performed given their diagnostic and
therapeutic benefit. ERCP allows for stent placement for palliating biliary obstruction, and EUS-guided fine needle aspiration (FNA) can provide tissue for pathological diagnosis. The role of PET/CT in this setting is evolving and has not yet been established. [13] Several biomarkers have also been tested for the diagnosis and management of pancreatic cancer. CA 19-9 is the only biomarker with usefulness in therapeutic monitoring and early detection of recurrent disease in patients with known pancreatic cancer. [14,15] However, it is not a specific biomarker and its level may be elevated in conditions such as cholestasis. Interestingly, patients who are negative for Lewis antigen A or B (approximately 10% of patients with pancreatic cancer) are unable to synthesize CA 19-9, even in advanced stages of the disease. [16]

Returning to our case

The patient’s CA19-9 was elevated at 2300 U/mL. After undergoing ERCP/EUS with successful biliary stent placement and FNA of the pancreatic mass, she was discharged from the hospital. An outpatient appointment with medical oncology was set up to review pathology and discuss further management. A week later, she was seen in the outpatient oncology clinic where her bilirubin improved to 1.0 gm/dL with normalization of alkaline phosphatase level. The FNA revealed a poorly differentiated pancreatic adenocarcinoma.

To summarize, we have a 64-year-old female with newly diagnosed metastatic pancreatic adenocarcinoma presenting as obstructive painless jaundice relieved by biliary stenting. She has minor comorbidities and an ECOG performance status of 1.

Which of the following is an appropriate initial systemic therapy?

A. Gemcitabine
B. Gemcitabine + erlotinib
C. Gemcitabine + nab-paclitaxel
D. Folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX)
E. C or D

FIRST-LINE THERAPY FOR METASTATIC PANCREATIC CANCER

Metastatic pancreatic cancer has a dismal prognosis and the 5-year survival rate is only 2% [1] with 1-year survival rates of 17% to 23% reported in the gemcitabine alone era. [17] The introduction of combination chemotherapy regimens, FOLFIRINOX and gemcitabine plus nab-paclitaxel, has significantly improved outcomes and either should be considered as appropriate first-line therapy for good performance status patients. [13]
Guided by the encouraging results of a phase 1/2 study, Von Hoff, et al., conducted a phase 3 study to evaluate the efficacy and safety of the combination of albumin-bound paclitaxel (nab-paclitaxel) and gemcitabine versus gemcitabine monotherapy in patients with metastatic pancreatic cancer (MPACT or Metastatic Pancreatic Adenocarcinoma Clinical Trial). [18] This multicenter international study, randomized 861 patients with a Karnofsky performance-status score of 70 or more to either nab (albumin bound)-paclitaxel plus gemcitabine or gemcitabine monotherapy until disease progression. The primary endpoint was overall survival and secondary endpoints were progression-free survival and overall response rate. Patients who received the combination had improved overall and progression-free survival as well as better response rate compared to those receiving gemcitabine alone (Table 1). The improved outcome from the combination came with the expected increase in toxicities compared to gemcitabine alone (Table 2). The use of subsequent anticancer therapy was similar between the two groups (38% in the nab-paclitaxel–gemcitabine group and 42% in the gemcitabine group). The trial was conducted internationally (North America, Europe and Australia). Approximately 10% of the patients were older than 75 years of age and 8% had a relatively poorer performance status (Karnofsky score = 70).

**Table 1. Efficacy Analysis in the Intention-to-Treat Population**

<table>
<thead>
<tr>
<th></th>
<th>MPACT Trial</th>
<th>ACCORD 11/PRODIGE</th>
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<tbody>
<tr>
<td></td>
<td>Gemcitabine + Nab-paclitaxel</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>ORR</td>
<td>23%</td>
<td>7%</td>
</tr>
<tr>
<td>PFS</td>
<td>5.5 m</td>
<td>3.7 m</td>
</tr>
<tr>
<td>OS</td>
<td>8.5 m</td>
<td>6.7 m</td>
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<tr>
<td>OS at 1 year</td>
<td>35%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Table 2. Common Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>MPACT Trial</th>
<th>ACCORD 11/PRODIGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine + Nab-paclitaxel</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Grade 3/4 neutropenia</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>1%</td>
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* Statistically significant difference

ORR=overall response rate; PFS=progression-free survival; OS=overall survival

Prior to presentation of the MPACT trial, researchers in France were studying the combination of 5FU, oxaliplatin and irinotecan (FOLFIRINOX) in advanced pancreatic cancer. Initial promising phase 1/2 data led to a multicenter, randomized, phase 2/3 trial, conducted at 48 centers in France (ACCORD 11/PRODIGE study) [19] in which 342 patients were randomly assigned to receive FOLFIRINOX or gemcitabine within 1 week after enrollment. Patients had to be ≤75 years of age, have a performance status of ECOG 0 to 1, and be treatment-naïve for metastatic disease. Duration of therapy goal was set at 6 months. Primary endpoint was overall survival and secondary endpoints were progression-free survival, tumor response, safety, and quality of life. The multidrug combination was found to be significantly more efficacious than gemcitabine as summarized in Table 1. With a median followup of 26.6 months, the median overall survival was better in the FOLFIRINOX group as compared with the gemcitabine group, and landmark overall survival rates at 6, 12, and 18 months were 75.9%, 48.4%, and 18.6%, respectively, in the FOLFIRINOX group as compared with 57.6%, 20.6%, and 6.0%, respectively, in the gemcitabine group. However, FOLFIRINOX was significantly more toxic than gemcitabine, as shown in Table 2. Incidences of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were significantly higher in the FOLFIRINOX group, whereas the incidence of grade 3 or 4 transaminitis was significantly higher in the gemcitabine group. Second-line therapy was administered in 47% patients in the FOLFIRINOX group and in 50% in the gemcitabine group. Significant improvement in the time until definitive deterioration in the quality of life was also noted in the FOLFIRINOX arm. Of note, the patient-selection criteria of this study were very rigorous (ECOG 0-1, age <76). Only 38% of the patients had carcinoma
of the pancreatic head, likely related to the exclusion of patients with a high bilirubin level, resulting in a lower proportion of enrolled patients with biliary stents (14.3%).

Thus, there are currently two appropriate combination regimens for frontline therapy for good performance status patients with metastatic pancreatic cancer. Both gem/nab-paclitaxel and FOLFIRINOX have data demonstrating superiority to the historical standard gemcitabine. However, they have not been compared head to head. Currently, there are no predictive biomarkers that can guide selection of FOLFIRINOX versus gem/nab-paclitaxel as initial therapy, and thus treatment should be individualized and based on patient’s age, performance status, and preferences. Other chemotherapy options including gemcitabine plus erlotinib, or gemcitabine monotherapy may be considered in patients with poor or compromised performance status.

After discussing the efficacy and safety results of these two landmark trials, our patient was treated with gemcitabine and nab-paclitaxel for first-line treatment of metastatic pancreatic cancer. Therapy was reasonably well tolerated in that she had fatigue requiring dose modification of nab-paclitaxel to 100 mg/m² and gemcitabine 1000 mg/m² after the first cycle. She did not develop any febrile neutropenia or require hospital admission. Other grade 1-2 adverse events included anemia, thrombocytopenia, diarrhea, transaminitis and nausea. Disease assessment at 8 weeks was performed with CT chest/abdomen/pelvis and repeat CA 19-9 assay. The largest liver lesion now measured 2.6 cm and overall there was a partial response per RECIST1.1. CA 19-9 was also lower at 1220 U/mL. She continued treatment for another 8 weeks with good tolerability at modified dosing. Imaging at 16 weeks showed continued partial response and CA 19-9 improved to 54 U/mL. Hence, she proceeded with 2 more cycles for a total of 6 months of therapy. At a clinic visit before the start of seventh cycle, she indicated increasing fatigue, dyspnea on exertion and weight loss of 8 lbs. She was still fully functional. CT chest abdomen and pelvis obtained just prior to the visit showed new multiple pulmonary nodules and increasing hepatic metastases consistent with disease progression. CA 19-9 had increased to 350 U/mL from a nadir of 54 U/mL.

What would you offer this patient now?
A. FOLFOX
B. FOLFIRINOX
C. FOLFIRI
D. 5-FU
E. Something else
Are there data to support second-line therapy in metastatic pancreatic cancer?

Currently there is no FDA approved second-line therapy for metastatic pancreatic cancer. The strongest data come from the CONKO-003 study which was a multicenter, randomized trial that studied a folic acid and fluorouracil/oxaliplatin combination (OFF) versus folic acid and fluorouracil (FF) in 168 gemcitabine refractory metastatic pancreatic cancer patients. [20] The median overall survival in the OFF arm was significantly better compared to the FF arm (5.9 months and 3.3 months, respectively, hazard ratio 0.66; 95% CI, 0.48-0.91; \( P = .010 \)). Toxicities were similar between the treatment arms, with the exception of grade 1-2 neurotoxicity (38.2% vs 7.1%, \( P < .001 \)). Gemcitabine-based second-line regimens for patients receiving FOLFIRINOX in first-line have not been as well studied. On balance, NCCN guidelines reflect common treatment patterns and recommend second-line fluoropyrimidine-based chemotherapy for those previously treated with gemcitabine-based therapy, and second-line gemcitabine-based therapy for those previously treated with fluoropyrimidine-based therapy. [13]

Extrapolating from the CONKO-003 study, we treated our patient with second-line mFOLFOX and she had a partial response on first imaging at 8 weeks. By the time she completed 5 cycles she had clinical progression with increasing right upper quadrant pain and fatigue. She still maintained a good performance status (ECOG 1) and was interested in further cancer directed therapy.

**FUTURE DIRECTIONS**

Although some progress has been made in the treatment of metastatic pancreatic cancer, median survival for patients with good functional status is still under one year. Thus, there is significant room for improvement. More recently, a large three-arm phase 3 study, NAPOLI-1, comparing single-agent MM398 (nanoliposomal irinotecan) to infusional 5-fluorouracil (5-FU) and the combination of MM398 plus 5-FU found improved outcome with the combination in patients with gemcitabine-refractory metastatic pancreatic cancer compared to 5FU alone (median OS was 6.1 months and 4.2 months, respectively, \( HR = 0.67, P = .012 \)). MM398 monotherapy did not improve overall survival when compared to 5-FU (median OS was 4.9 and 4.2 months, respectively, \( HR 0.99, P = .94 \)) [21]. This agent is expected to be approved in the future for refractory pancreatic cancer, likely in combination with 5-FU.

Several other agents are in phase 3 evaluation, building upon promising phase 1/2 data. Fractionated radioimmunotherapy with (90) Y-clivatuzumab tetraxetan (90Y-hPAM4, humanized monoclonal antibody targeting a mucin antigen expressed in most pancreatic cancers) and low-dose gemcitabine has shown promise in the phase 1/2
setting [22] and has now entered phase 3 testing in the third-line setting (NCT01956812). The study design is low-dose gemcitabine + Y90 vs. low-dose gemcitabine plus placebo with a 2:1 randomization. Another drug, ruxolitinib, a JAK 1/2 inhibitor, has been tested in refractory disease in combination with capecitabine vs capecitabine plus placebo in a randomized phase 2 study. [23] In a pre-specified subgroup of patients with systemic inflammation as measured by elevated serum C-reactive protein (CRP >13 mg/L), survival significantly favored capecitabine + ruxolitinib over capecitabine + placebo. In this subgroup, 3 and 6 month survival were 48% and 42% with ruxolitinib vs 29% and 11% with placebo, respectively. These encouraging results have led to the currently enrolling phase 3 JANUS 1 study with a similar study design but restricted to patients with elevated CRP (NCT02117479). Evofosfamide (formerly TH-302) is a prodrug that converts into a DNA alkylating agent in the hypoxic tumor microenvironment. Initial studies combining it with gemcitabine suggested improvement in progression free survival compared to gemcitabine alone (5.6 months vs 3.6 months; P = .005) and a non-significant trend towards better overall survival (9.2 months vs 6.9 months, P = .8). [24] A phase 3 trial of gemcitabine +/- TH-302 has completed accrual and efficacy results are awaited.

Pancreatic cancer is associated with a dense tumor stroma which may promote tumor growth and limit chemotherapy perfusion. PEGylated recombinant human hyaluronidase, PEGPH20, depletes hyaluronan (HA) in tumors and is being investigated in pancreatic cancer with chemotherapy. In a recently reported randomized phase 2 study of nab-paclitaxel + gemcitabine with or without PEGPH20 in treatment-naïve metastatic pancreatic cancer patients, progression-free survival favored the combination in tumors with high HA levels (median PFS was 9.2 months and 4.8 months, for high and low HA levels respectively, P = .03). [25] A follow-up phase 3 study in the high HA population is planned. Another promising avenue of clinical research in pancreatic cancer is the use of immune targeted therapy and checkpoint inhibitors. Checkpoint inhibitors, including agents that alter immune suppressive signals in other human cancers, have failed to demonstrate objective responses when given as single agents to pancreatic cancer patients. [26] There is some evidence that immunosuppressive pathways, including regulatory T-cells and CTLA-4 expression on T-cells, can be overcome by the addition of vaccine and low-dose cyclophosphamide to PD-1 blockade, supporting combination strategies. [27] GVAX pancreas (granulocyte-macrophage colony-stimulating factor-secreting allogeneic pancreatic tumor cells) induces T-cell immunity to cancer antigens, including mesothelin, that are overexpressed in pancreatic cancer cells. Low-dose cyclophosphamide (Cy), administered with GVAX, can inhibit regulatory T-cells. Another cancer vaccine, CRS-207 (live-attenuated listeria monocytogenes—expressing mesothelin) induces innate and adaptive immunity. GVAX and CRS-207 vaccines have been evaluated in pancreatic cancer. In a recently reported phase 2 study, previously treated mPC patients were
randomly assigned to either Cy/GVAX followed by four doses of CRS-207 or six doses of Cy/GVAX. Addition of CRS-207 to Cy/GVAX improved overall survival in this study (Median OS 6.1 months versus 3.9 months, HR 0.59; P = .02). [28]

Our patient decided to participate in a phase 1 study but she developed infectious complications from biliary obstruction requiring ICU admission, antibiotics and placement of percutaneous biliary drains. She recovered to some extent but had a significant decline in her performance status and worsening pain related to disease progression. Hence, the patient and her family were counseled and she was transitioned to hospice care.

Summary

First-line therapy for metastatic pancreatic cancer has evolved over time to include combination chemotherapies with strong evidence backing the use of gemcitabine + nab-paclitaxel and FOLFIRINOX. Both regimens are appropriate for first-line therapy, and choice is guided by physician and patient preference and the unique side-effect profile of each regimen. There are fewer data in second-line, but the alternative regimen not chosen for first-line is often utilized for patients with preserved performance status. Increasing avenues of research across many areas of investigation bode well for future developments to treat this deadly disease.

References


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