At-A-Glance: Management of Advanced Pancreatic Cancer

Background
Pancreatic cancer is the fourth leading cause of cancer-related death in the United States, with more than 44,330 deaths estimated for 2018.[1] This summary discusses cancer of the exocrine pancreas, which represents > 95% of pancreatic cancers. This handout is intended as a brief overview of advanced pancreatic cancer, recommended systemic therapy, and management of disease-related and treatment-related adverse events.

Staging and Diagnosis
- < 10% of patients present with potentially resectable disease; approximately 56% present with metastatic disease[1]
- Staging based on TNM system along with resectability and extent of resection[2]
- CT scan most commonly used imaging modality for diagnosis; MRI appropriate alternative with PET/CT consideration[3]
- Endoscopic ultrasound-directed fine-needle aspiration biopsy preferred over CT-guided approach for sampling a pancreatic mass[3]
  - In metastatic setting, biopsy of metastasis (eg, liver lesion) is usually safer
- EUS may be useful for staging, especially in patients being considered for surgery[4]
- CA19-9 may be useful for diagnosis, staging, determining resectability, assessing treatment response[3]

Clinical Presentation
- Pancreatic cancer often has no early signs or symptoms[4]
- Presenting signs and symptoms can include weight loss, jaundice, nausea, and depression in > 70% of patients[1,5]
- Metastasis common in lymph nodes, liver, and lung

Chemotherapeutic Treatment of Advanced Pancreatic Cancer[6]
- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged
- Performance status (PS) critical in selecting treatment for advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Performance Status</th>
<th>Benefit From Combination Therapy?</th>
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<tbody>
<tr>
<td>ECOG PS 0-1/KPS 90% to 100%</td>
<td>Yes (HR: 0.76; P &lt; .0001)</td>
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<tr>
<td>ECOG PS 2/KPS 60% to 80%</td>
<td>No (HR: 1.08; P = .40)</td>
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First-line Gemcitabine-Based Therapy
- Gemcitabine: first drug approved for use in metastatic disease setting based on improvements in survival and PS as well as decreased pain vs controls[7]
- Albumin-bound (nab) paclitaxel in combination with gemcitabine is associated with improved survival and overall response rates vs gemcitabine monotherapy and the combination is recommended as first-line therapy[8]
  - Gemcitabine 1000 mg/m² IV + albumin-bound paclitaxel at 125 mg/m² IV (both agents administered weekly x 3 of 4)
  - Recommended for patients of all ages with ECOG PS 0-2

First-line FOLFIRINOX Therapy
- FOLFIRINOX associated with improved survival and overall response rates vs gemcitabine monotherapy and recommended as first-line therapy[8]
  - FOLFIRINOX associated with higher rates of grade 3/4 toxicities, including neutropenia, febrile neutropenia, fatigue, diarrhea
  - Better tolerated in younger, fit patients; not recommended in patients older than 75 years of age or those with ECOG PS ≥ 2[8]
- FOLFIRINOX dosage and administration[9]
  - Oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², fluorouracil 400 mg/m² bolus or 2400 mg/m² IV over 48 hours

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Second-line Chemotherapy for Metastatic Pancreatic Adenocarcinoma

After Gemcitabine-Based Regimen
- Nanoliposomal formulation of irinotecan (MM-398) in combination with 5-FU and leucovorin recommended for the treatment of patients (PS 0/1) with metastatic adenocarcinoma of the pancreas after disease progression\(^ \text{[10,11]} \)
- 5-FU/leucovorin + oxaliplatin or irinotecan may also be considered in patients with PS 0/1. 5-FU monotherapy or best supportive care should be considered for patients with PS 2\(^ \text{[10]} \)

After FOLFIRINOX
- For patients with PS 0/1, gemcitabine/albunin-bound paclitaxel. For patients with PS 2, gemcitabine monotherapy or best supportive care\(^ \text{[10]} \)

Investigational Agents for Pancreatic Cancer

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Stromal-depleting agents</td>
<td>PEGPH20 (recombinant hyaluronidase)</td>
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<tr>
<td></td>
<td>Vitamin D analogues</td>
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<tr>
<td>Immunotherapies</td>
<td>Anti-CD40 mAbs</td>
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<td></td>
<td>CAR T-cells</td>
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<td></td>
<td>IDO inhibitors</td>
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<td></td>
<td>Immune checkpoint inhibitors (antibodies against CTLA-4, PD-1, PD-L1)</td>
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<tr>
<td>Signal transduction inhibitors</td>
<td>BTK inhibitors (eg, ibrutinib)</td>
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<tr>
<td></td>
<td>Bispecific anti-IGFR/HER3 mAbs (eg, istiratumab)</td>
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<td></td>
<td>PARP inhibitors (eg, olaparib)</td>
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<tr>
<td></td>
<td>STAT3 inhibitors (eg, napabucasin [BBI608])</td>
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Management of Common Adverse Events: Albumin-Bound Paclitaxel and Gemcitabine\(^ \text{[12]} \)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Albumin-Bound Paclitaxel/Gemcitabine</th>
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<tbody>
<tr>
<td>Grade 3/4 febrile neutropenia</td>
<td>Withhold albumin-bound paclitaxel/gemcitabine until fever resolves and ANC ≥ 1500 cells/mm(^3); resume at next lower dose level</td>
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<tr>
<td>Grade 3/4 peripheral neuropathy</td>
<td>Withhold albumin-bound paclitaxel/gemcitabine until peripheral neuropathy improves to grade ≤ 1; resume at next lower dose level</td>
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<tr>
<td></td>
<td>No dose reduction in gemcitabine</td>
</tr>
<tr>
<td>Grade 2/3 cutaneous toxicity</td>
<td>Reduce to next lower dose level of albumin-bound paclitaxel/gemcitabine; discontinue treatment if toxicity persists</td>
</tr>
<tr>
<td>GI toxicity; grade 3 mucositis or diarrhea</td>
<td>Withhold albumin-bound paclitaxel/gemcitabine until grade ≤ 1; resume at next lower dose level</td>
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Hypersensitivity
- Severe and sometimes fatal hypersensitivity reactions have been reported
  - Do not rechallenge after a severe hypersensitivity reaction

Pneumonitis
- Occurs in ~ 4% of patients receiving albumin-bound paclitaxel/gemcitabine
  - Monitor for signs and symptoms of pneumonitis
  - Interrupt albumin-bound paclitaxel/gemcitabine during evaluation of suspected pneumonitis

Nervous system
- Sensory neuropathy is dose and schedule dependent
  - Grade 1/2 sensory neuropathy does not generally require dose modification
  - With grade ≥ 3 sensory neuropathy, withhold treatment until resolution to grade 1 followed by a dose reduction for subsequent courses

ANC, absolute neutrophil count.

Management of Hematologic Adverse Events: Albumin-Bound Paclitaxel and Gemcitabine\(^ \text{[12]} \)
- Bone marrow suppression (primarily neutropenia) is dose dependent and a dose-limiting toxicity
  - Delay, reduce, or withhold doses as needed
- In clinical studies, grade 3/4 neutropenia occurred in 38% of patients with pancreatic cancer
## Management of Adverse Events: FOLFIRINOX

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Management</th>
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</table>
| **Diarrhea/GI toxicity**      | - Early diarrhea usually transient, treat with atropine. **Late diarrhea** (≥ 24 hrs after injection) may be life threatening; treat promptly with loperamide, fluids, and electrolytes  
- Delay chemotherapy until pretreatment bowel ≥ 24 hrs without need for antidiarrheal medication; if grade 2-4 late diarrhea occurs, treat and decrease subsequent doses in current cycle  
- Delay treatment and reduce dose after recovery from grade 3/4 GI toxicities  |
| **Peripheral neuropathy**     | - Reduce dose if persistent grade 2 neurosensory events do not resolve; consider discontinuing oxaliplatin if persistent grade 3 neurosensory events  |
| **Neutropenia**               | - Omit irinotecan during a cycle if neutropenic fever occurs or if ANC < 1000/mm³; after patient recovers to ANC ≥ 1000/mm³, subsequent doses should be reduced depending on the level of neutropenia observed  
- Delay until neutrophils ≥ 1.5 x 10⁹/L after grade 4 neutropenia or febrile neutropenia and reduce next dose  |
| **Thrombocytopenia**          | - Delay until platelets ≥ 75 x 10⁹/L after grade 3/4 thrombocytopenia and reduce next dose  |

### Management of Disease-Related Adverse Events

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<th>Adverse Event</th>
<th>Management</th>
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<tr>
<td>Biliary and gastric outlet obstruction</td>
<td>Surgical intervention for palliative bypass or placement of biliary and/or duodenal stents</td>
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<tr>
<td>Pain</td>
<td>Narcotic analgesics, radiation, or celiac plexus neurolysis[16-18]</td>
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<tr>
<td>Cachexia, anorexia, weight loss</td>
<td>Nutritional consult, supplements, and pharmacologic appetite stimulants[19]</td>
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<tr>
<td>Depression</td>
<td>Psychiatric consultation</td>
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<tr>
<td>Venous thromboembolism</td>
<td>Prophylactic enoxaparin[20,21]</td>
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<tr>
<td>Fluid retention, ascites</td>
<td>Diuretics, compression stockings, paracentesis, percutaneous peritoneal drain</td>
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### The Role of Early Palliative Care

- Early referral to palliative care has been shown to be beneficial in advanced cancer. The pivotal trial by Temel and colleagues[22] showed fewer medical interventions, improved quality of life, decreased anxiety and depression, and **improved survival**

### References


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