Pancreatic Adenocarcinomas and Endocrine Cancers

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Learning Objectives

1. Evaluate the role that risk factors play in the development of pancreatic adenocarcinoma.
2. Evaluate the effect of patient characteristics such as performance status, age, and comorbidities on treatment decisions for patients with pancreatic adenocarcinomas or endocrine cancers.
3. Discuss adverse effects of the drug therapies and the supportive care used in the management of pancreatic adenocarcinoma.
4. Develop an appropriate treatment plan for a patient with newly diagnosed pancreatic adenocarcinoma.
5. Distinguish the difference in treatment and prognosis in patients with resectable and unresectable pancreatic adenocarcinoma.
6. Assess the role of adjuvant and neoadjuvant therapy in advanced stage pancreatic adenocarcinoma.
7. Evaluate the role of various hormones in the pathophysiology and clinical presentation of endocrine tumors.
8. Assess the role of chemotherapy in the treatment of endocrine tumors.

Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is one of the deadliest cancers. Although it accounts for only 3% of all cancer diagnoses, pancreatic adenocarcinoma is the fourth most common cause of cancer-related death in both men and women in the United States. The American Cancer Society estimated that 43,140 new cases of pancreatic cancer with 36,800 deaths would occur during 2010 in the United States.

Pancreatic ductal adenocarcinomas arise from the exocrine cells of the pancreas and are the most common type of pancreatic tumor, constituting about 95% of all pancreatic tumors. Thus, pancreatic adenocarcinoma is often used synonymously with pancreatic cancer in both clinical practice and oncology literature. The annual incidence of pancreatic adenocarcinoma in the United States is on the rise, with projections increasing from about 40,000 in 2010 to 62,000 in 2030. Regardless of therapy, the 5-year overall survival (OS) for all stages is only 3%. Median survival for patients with locally advanced and metastatic disease is 8–12 months and 3–6 months, respectively, and 90% of all patients die within 1 year of diagnosis.

Risk Factors

Many risk factors are associated with the development of pancreatic adenocarcinoma, some of which are modifiable. One major modifiable risk factor is smoking, which is thought to contribute to 2–3 of every 10 cases. Smokers have a 2.5-fold higher risk of developing

Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605–17.
- Royal RE, Wolff RA, Crane CH. Pancreatic cancer. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Devita, Hellman and Rosenberg's Cancer: Principles and Practice of Oncology, 8th ed. Philadelphia: Lippincott, Williams & Wilkins, 2008:1087–124.
- Wells SA Jr. Cancer of the endocrine system. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Devita, Hellman and Rosenberg's Cancer: Principles and Practice of Oncology, 8th ed. Philadelphia: Lippincott, Williams & Wilkins, 2008:1656–740.

Abbreviations in This Chapter

5-HIAA	5-hydroxyindoleacetic acid
BSC	Best supportive care
EGFR	Epidermal growth factor receptor
FDR	Fixed-dose rate
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PET	Pancreatic endocrine tumor
PFS	Progression-free survival
PS	Performance status
QoL	Quality of life
VTE	Venous thromboembolism

pancreatic adenocarcinoma in comparison with nonsmokers. Using smokeless tobacco can also increase this risk. Obesity and lack of exercise elevate the risk over 1.5 times, especially for those with a body mass index of 30 kg/m^2 or more. Infection with *Helicobacter pylori* (especially the Cag A–positive strain) has also been associated with a 2-fold higher risk in the general population. Other modifiable risk factors with conflicting data include a diet high in fat and meat, coffee and alcohol consumption, and aspirin and nonsteroidal anti-inflammatory drug use.

Nonmodifiable risk factors include older age (mean age at diagnosis, 72 years), male sex, and African American race. Patients with type 1 diabetes have a 2-fold increased risk. Other risk factors include chronic pancreatitis, cirrhosis of the liver, past partial gastrectomy, cholecystectomy, and exposure to some pesticides, dyes, and chemicals. Some familial cancer syndromes are associated with an increased risk, although these account for only 5% to 10% of patients with pancreatic adenocarcinoma. These include hereditary chronic pancreatitis, inherited breast cancer, and familial adenomatous polyposis (Lynch syndrome).

Screening and Prevention

No preventive strategies are available beyond avoiding and modifying risk factors. Because more than 75% of all patients with pancreatic adenocarcinoma are diagnosed with locally advanced or metastatic disease, screening could play an important role in earlier detection. No screening guidelines are available for the general population, although some imaging modalities may be of use in high-risk individuals such as those with a first-degree relative with pancreatic adenocarcinoma or patients with inherited syndromes. Studies are ongoing to evaluate the specificity of endoscopic ultrasonography, and these high-risk individuals are encouraged to enroll in clinical trials investigating potential screening tools.

Pancreatic adenocarcinoma produces several tumor markers (proteins) that are detectable in the bloodstream (e.g., antigens CEA, CA 19-9, CA 125). Concentrations of CA 19-9 are elevated in 90% of patients with pancreatic adenocarcinoma at diagnosis, but the sensitivity is only about 20% in early stage tumors. It has a low specificity because it is elevated in other malignancies (e.g., colorectal cancer) and can be falsely positive in patients with benign biliary obstruction. Also, 5% to 15% of the general population cannot synthesize CA 19-9 (Lewis antigen–negative individuals), leading to false-negative results. Although CA 19-9 is a poor antigen for detecting disease, serial CA 19-9 concentrations may be measured during therapy because changes may correlate with prognosis. For patients with hyperbilirubinemia, CA 19-9 levels should be drawn after the bile duct has been decompressed. Testing methodology for the CA 19-9 antigen is not standardized and different commercial methods are available. Results from one testing method cannot be compared with another.

Diagnosis and Staging

Clinical Presentation

Symptoms of pancreatic adenocarcinoma are often vague and may delay diagnosis of the disease for several months. Signs and symptoms of pancreatic adenocarcinoma may include pain, jaundice, weight loss, digestive problems, and depression. Less common signs include Virchow node (left supraclavicular lymphadenopathy), venous thromboembolism (VTE), ascites, and panniculitis (subcutaneous nodes with fat necrosis), all of which typically indicate advanced or metastatic disease. New-onset diabetes may precede a diagnosis of pancreatic adenocarcinoma. One study found that 1% of patients older than 50 with new-onset diabetes developed pancreatic adenocarcinoma within 3 years.

Some presenting symptoms may be associated with tumor location. About two-thirds of adenocarcinomas originate in the head of the pancreas, with the remainder arising in the body or tail. Tumors not located in the head of the pancreas are less likely to cause early symptoms and are more often diagnosed when advanced disease is present. Biliary obstruction occurs in up to 70% of patients with tumors in the head of the pancreas, with jaundice often the presenting sign. Eighty percent of patients with locally advanced or metastatic disease present with pain. Weight loss can be significant in patients with pancreatic adenocarcinoma and is associated with anorexia, steatorrhea, diarrhea, and early satiety.

Staging and Prognosis

Pancreatic adenocarcinoma staging is based on the American Joint Committee on Cancer criteria. Tumor size, nodal status, and presence of metastases make up the basic criteria, although treatment is more commonly

based on whether the tumor can be surgically resected. Appropriate imaging is necessary to determine the location of cancer within the pancreas and the extension of disease outside of the pancreas. Ultrasonography and computed tomography, as well as magnetic resonance imaging, may be used to accurately visualize and stage the cancer. However, determining the true extent of cancer spread may require surgical inspection.

Tumors are categorized as resectable, locally advanced unresectable, or metastatic. The best prognosis occurs in tumors confined within the pancreas, which are usually resectable. However, only 10% of patients present with early stage cancers. Local metastases are most common in the surrounding lymph nodes; distant metastases are often seen in the liver, peritoneal surfaces, and, more rarely, the lung. Poor prognostic factors include lymph node metastases, less-differentiated tumor cells, high concentrations of CA 19-9, persistently elevated CA 19-9 after surgery and/or chemotherapy, and positive margins at resection. Patients with clear surgical margins and small tumor size (less than 2 cm) have a more favorable prognosis, although 5-year survival for tumors with favorable prognostic characteristics is still only 18% to 24%. Only one-half of patients with resectable disease will still be alive at 2 years.

Treatment

Complete resection is the only potentially curative treatment. Surgery, radiation, and chemotherapy all play a role, depending on the goals of therapy. Early stage tumors confined within the pancreas can be surgically removed, although there is still a high rate of recurrence. Radiation and/or chemotherapy are usually given after surgery. Systemic drug therapy alone is used in patients with advanced and metastatic disease with the goal of increasing survival time and controlling symptoms. Enrollment in a clinical trial is a reasonable option for many patients with good performance status (PS). Table 1-1 describes the grading system for PS.

Surgery for pancreatic adenocarcinoma may be either curative or palliative. Although it is the only potentially curative treatment, less than 20% of patients are candidates for surgery at the time of diagnosis. Surgeries include pancreatoduodenectomy (also called the Whipple procedure), distal pancreatectomy, and total pancreatectomy. Surgery may also be attempted palliatively to relieve pain and other symptoms of disease such as bile duct obstruction.

In almost all surgical candidates, radiation therapy is used either before or after surgery because of the high risk of locoregional recurrence, even when there is a good surgical resection. Chemotherapy is usually given before or in conjunction with radiation, and this combination is standard in resectable disease (Table 1-2). If it is uncertain whether surgery can completely remove all tumor, preoperative radiation may allow for a more complete resection in a borderline resectable locally advanced tumor.

Chemotherapy and Chemoradiation in Resectable Disease

Both fluorouracil and gemcitabine single-agent therapy after surgical excision result in improvement in progression-free survival (PFS) and OS compared with surgery alone. A phase III trial randomized patients after surgical resection to treatment with either fluorouracil plus leucovorin or single-agent gemcitabine versus observation for 6 months. The observation arm was halted early because of inferior results, and the study continued with the two treatment arms. Overall survival was comparable for both agents (i.e., 23 months with fluorouracil/leucovorin, 23.6 months with gemcitabine). This confirmed the role of adjuvant chemotherapy but did not establish the advantage of one agent over the other.

Table 1-1. Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active; able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

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Table 1-2. Common Chemotherapy Regimens for Metastatic Pancreatic Adenocarcinoma

Drug	Dose	Schedule
Gemcitabine	1000 mg/m^2 over 30 minutes	Weekly x 7 weeks, 1 week break, then days 1, 8, 15 every 28 days
Gemcitabine FDR	1500 mg/m^2 over 150 minutes	Days 1, 8, 15 every 28 days
Gemcitabine + erlotinib	1000 mg/m^2 over 30 minutes 100 mg orally	Weekly x 7 weeks, 1 week break, then days 1, 8, 15 every 28 days Daily
Gemcitabine + cisplatin	1000 mg/m^2 over 30 minutes 50 mg/m^2 over 1 hour	Days 1, 15 every 28 days
Gemcitabine FDR + oxaliplatin	1000 mg/m^2 over 100 minutes 100 mg/m^2 over 2 hours	Every 14 days
Capecitabine	1000 mg/m^2 two times/day	Days 1-14 every 28 days
Gemcitabine + capecitabine	1000 mg/m^2 over 30 minutes 650 mg/m^2 orally two times/day	Days 1, 8 Days 1–14 Every 21 days
Oxaliplatin + fluorouracil + leucovorin	85 mg/m^2 over 2 hours 2000 mg/m^2 over 24 hours 200 mg/m^2 over 30 minutes	Days 8, 22 Days 1, 8, 15, 22 Days 1, 8, 15, 22 Every 42 days
Capecitabine + oxaliplatin	1000 mg/m^2 two times/day 130 mg/m^2 over 2 hours	Days 1–14 every 28 days Every 21 days
Fluorouracil + leucovorin	2000 mg/m^2 over 24 hours 200 mg/m^2 over 30 minutes	Days 1, 8, 15, 22 every 42 days Every 42 days
Oxaliplatin + irinotecan + leucovorin+ fluorouracil + fluorouracil	85 mg/m^2 over 2 hours 180 mg/m^2 over 30-90 minutes 400 mg/m^2 over 30-90 minutes 400 mg/m^2 over 30-90 minutes 1200 mg/m^2 over 24 hours x 2 days	Every 14 days

FDR = fixed dose regimen; XRT=radiation therapy.

Several studies have shown the benefit of concurrent use of chemotherapy with radiation (chemoradiation), either pre- or postoperatively, in patients with resectable pancreatic adenocarcinoma. Postoperative chemoradiation with fluorouracil or gemcitabine is a recommended therapy, although questions remain regarding which patients receive the most benefit. One early study demonstrated a significant difference in median survival (i.e., 20 months in patients treated with chemoradiation vs. 11 months in patients treated with surgery alone). These results were considered to be validated because another study found a median survival of 17 months following chemoradiation compared with 13 months in patients treated with surgery alone, although this difference was not statistically significant.

A phase II study of radiation and chemotherapy with combined cisplatin, interferon alfa, and fluorouracil resulted in a median survival of 27.1 months, the longest reported yet. However, this survival benefit was offset by significant toxicities, with only 56% of patients completing the entire treatment course.

The use of additional postoperative chemotherapy beyond the standard of care in resectable patients was evaluated in a study looking at gemcitabine versus fluorouracil. After surgery, patients were randomized to receive gemcitabine or fluorouracil for the duration of treatment, receiving the assigned chemotherapy alone for 3 weeks. About 2 weeks later, continuous infusion fluorouracil was given in conjunction with radiation. This was followed 3–5 weeks later with the assigned gemcitabine or fluorouracil for an additional 12 weeks. The addition of gemcitabine chemotherapy before and after fluorouracil-based chemoradiation increased median survival, although this was not statistically significant. Overall, postsurgical treatment with gemcitabine followed by fluorouracil-based chemoradiation is considered the standard of care for patients with resectable disease. Gemcitabine alone may be used in patients who will not tolerate more intense therapy.

The newer approach of giving preoperative radiation combined with fluorouracil or gemcitabine (neoadjuvant approach) is being studied in phase II trials. Neoadjuvant chemoradiation may decrease the rate of locoregional recurrence and positive margins after surgery. It may also convert a patient with a borderline resectable tumor to resectable status. In one study, 60% to 80% of lesions could be completely resected 4–6 weeks after completion of chemoradiation therapy, with patients experiencing an improved median survival of 16–36 months. No phase III trials have been conducted to compare these treatments preoperatively versus postoperatively.

Chemotherapy and Chemoradiation in Unresectable Disease

Chemotherapy is considered a standard treatment option in all patients with unresectable or metastatic disease. Several randomized trials have shown that chemoradiation therapy is superior to chemotherapy alone, although it is associated with more adverse effects. The use of chemotherapy with radiation has to be weighed against potential toxicities and complications. Thus, a patient's quality of life (QoL) should be an important end point in studies evaluating the use of chemotherapy in patients with unresectable pancreatic adenocarcinoma.

Monotherapy

Many investigators have attempted to improve upon the minimal ability of chemotherapy to improve survival in advanced and metastatic pancreatic cancer. Fluorouracil was the standard of care until 1997, when a study comparing gemcitabine to fluorouracil found the 12-month survival rate for patients treated with gemcitabine increased to 18% compared with 2% in patients treated with fluorouracil. Gemcitabine was also found to provide clinical benefit compared with fluorouracil in measures of QoL such as pain, PS, and weight changes. Gemcitabine chemotherapy, with or without radiation therapy, remains the standard of care because of its effect on QoL and palliation of symptoms in patients with advanced and metastatic pancreatic adenocarcinoma.

In an attempt to improve response, pharmacokinetic studies suggested that extending the infusion of gemcitabine might be beneficial. The intracellular activation to the phosphorylated form of gemcitabine is maximized at infusion rates of about 10 mg/m^2/minute. Several studies have looked at the efficacy of fixed-dose rates (FDRs) of 10 mg/m^2/minute versus the standard 30-minute infusion of gemcitabine and have found conflicting results. Despite the lack of a clear benefit, the current National Comprehensive Cancer Network (NCCN) guidelines suggest that FDR gemcitabine can be used as an alternative to standard infusions of gemcitabine.

Combination Therapy

With the success of gemcitabine, multiple studies have investigated the feasibility of adding other drugs to gemcitabine in hopes of improving response and survival. Phase II studies have investigated gemcitabine combined with cisplatin, oxaliplatin, capecitabine, irinotecan, or pemetrexed, as well as with targeted agents such as bevacizumab, erlotinib, or cetuximab. Ongoing phase II studies are evaluating a number of agents in combination with gemcitabine and radiation therapy for unresectable disease. These include the addition of oxaliplatin, bevacizumab, cetuximab, and erlotinib.

In phase III trials, gemcitabine combinations have consistently demonstrated outcomes similar to gemcitabine monotherapy, yielding a median OS of only 9–10 months. These discouraging results have brought to light changes needed for future clinical trials, including evaluating outcomes in subsets of patients. For example, studies should be designed to look specifically at patients with advanced versus metastatic cancer or those with a good versus poor PS. This will help obtain a more accurate understanding of the effects of the investigational therapy within patient subgroups.

A meta-analysis that included six randomized trials of gemcitabine in combination with fluorouracil or capecitabine in advanced disease demonstrated that the combinations prolonged OS, although the individual studies were all nonsignificant. The authors concluded that fluorouracil or capecitabine plus gemcitabine could be considered a new treatment option for these patients. Phase III trials individually have not shown a significant benefit of adding cisplatin or oxaliplatin to gemcitabine, but a pooled analysis showed a significant improvement in PFS and OS. Other studies have looked at FDR administration of gemcitabine in combination with cisplatin, oxaliplatin, docetaxel, or irinotecan but have not demonstrated significant benefit. Based on the pooled study and meta-analyses, fluoropyrimidines (e.g., fluorouracil, capecitabine) or platinum analogs (e.g., oxaliplatin, cisplatin) are reasonable options to add to gemcitabine in patients with advanced disease who have a good PS.

A phase III study's interim analysis was recently presented in abstract form, describing the first non–gemcitabine-containing regimen to show significant benefit against gemcitabine alone. The combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX regimen) produced an OS of 11.1 months versus 6.8 months with gemcitabine monotherapy. Although patients in the experimental arm only received an average of 75% of the doses, toxicities were considered to be manageable, and this combination can be considered in patients with a good PS.

Several studies have also evaluated targeted agents in the treatment of pancreatic adenocarcinoma. Erlotinib, an oral epidermal growth factor receptor (EGFR)

inhibitor, is the only agent that has shown a statistically significant improvement in OS when given in combination with gemcitabine in patients with advanced, unresectable or metastatic disease. However, median OS only increased 10–12 days, with the 1-year survival rate increasing by 5% with the addition of erlotinib. Adverse effects were higher in the combination group, consisting mainly of gastrointestinal symptoms and rash. Patients who develop grade 2 or greater rashes associated with the EGFR inhibitors had a greater median OS with an increase from 5.5 to 10.5 months. This efficacy correlation is similar to other diseases such as lung and colorectal cancer.

Questions remain regarding how clinically meaningful these results are and who will benefit most from the addition of erlotinib. However, as the only treatment that has demonstrated a statistically significant benefit over gemcitabine monotherapy, gemcitabine in conjunction with erlotinib is a first-line option in patients with a good PS and metastatic disease. Phase III trials of cetuximab, another EGFR inhibitor, and bevacizumab, a vascular endothelial growth factor inhibitor, failed to demonstrate any survival advantage in unresectable pancreatic cancer.

Questions remain regarding how clinically meaningful these results are and who will benefit most from the addition of erlotinib. However, as the only treatment that has demonstrated a statistically significant benefit, gemcitabine in conjunction with erlotinib is a first-line option in patients with a good PS and unresectable disease. Phase III trials of cetuximab, another EGFR inhibitor, and bevacizumab, a vascular endothelial growth factor inhibitor, failed to demonstrate any survival advantage in unresectable pancreatic cancer.

Second-line Therapy

Prognostic factors that help predict survival time after gemcitabine failure include time to disease progression following first-line therapy, PS, baseline CA 19-9, and serum albumin levels. Although second-line chemotherapy is indicated in patients with a good PS, there is no clear choice in patients with refractory disease. No randomized studies have assessed second-line therapy versus best supportive care (BSC) in patients with pancreatic adenocarcinoma, and clinical trials are recommended for all patients with refractory disease. If an investigational therapy is not available for a patient, several treatment options are available.

If a patient has not yet received fluorouracil/leucovorin or capecitabine therapy, these agents should be considered. However, other second-line agents have been investigated as well. Pemetrexed therapy resulted in a median OS of 20 weeks. Significant myelosuppression, diarrhea, nausea, and stomatitis occurred but were manageable. Weekly paclitaxel was also found to have activity, with a median survival time of 17.5 weeks. Myelosuppression, elevated transaminases, and alopecia occurred but were not severe. Use of oxaliplatin was associated with an improvement in tumor-related symptoms but did not decrease tumor size. Targeted agents currently in trials as second-line therapies include erlotinib, sunitinib, and everolimus, as well as several investigational agents.

Combination chemotherapy in patients with refractory disease after gemcitabine-based therapy includes mainly platinum-based agents or continuing gemcitabine in combination with other cytotoxic agents that have been studied as first-line therapies. Fluorouracil/leucovorin in combination with oxaliplatin has become a recommended second-line regimen in gemcitabine-refractory patients who have not had exposure to fluoropyrimidines. Results of a recent phase III trial demonstrated a significantly increased median OS with oxaliplatin plus fluorouracil/leucovorin (20 weeks) versus fluorouracil/leucovorin alone (13 weeks). Oxaliplatin in combination with capecitabine, irinotecan, pemetrexed, or cisplatin has also shown some benefit. Toxicities with combination chemotherapy regimens have been manageable. Some of the combinations with targeted agents being investigated are capecitabine and erlotinib, docetaxel and gefitinib, and bevacizumab and erlotinib.

Supportive Care

Complications of pancreatic adenocarcinoma to address include blockages of the bile duct, gastric outlet obstruction, pain, nutritional deficiencies, pancreatic insufficiency, and the risk of VTE. Biliary obstruction occurs in up to 70% of patients with pancreatic adenocarcinoma, most often with tumors located in the head of the pancreas. Jaundice, cholangitis, or pruritus may also be present. Preoperative biliary drainage can improve symptoms and liver function and should be considered if surgery is to be delayed because of neoadjuvant therapy. For patients who are not candidates for surgery, a biliary bypass may be done for palliative purposes. This procedure may also be performed in conjunction with other procedures that palliate symptoms resulting from gastric outlet obstruction or pain. Studies have not shown decompression and stenting to improve outcomes if done after surgery.

Cancer-related pain is experienced by many patients with locally advanced and metastatic pancreatic adenocarcinoma. The pain can acutely worsen, and the efficacy of the patient's analgesic regimen should be monitored closely. In addition to the usual treatment options of opioids, a celiac plexus block can improve pain relief with a decrease in opioid requirements and delay the decline in QoL.

Patients with pancreatic adenocarcinoma have a high risk of VTE (incidence of 10% to 20%). A low-molecular-weight heparin is the preferred treatment;

the incidence of recurrent VTE is one-half that of patients receiving oral anticoagulation.

Nutritional status should be addressed in all patients with pancreatic adenocarcinoma to maintain the best possible QoL. Patients may have debilitating gastric symptoms, gastric obstruction, or lack a fully functioning pancreas, any of which can compromise nutritional status. Surgical resection of the pancreas or tumor-induced damage may lead to a decreased excretion of digestive enzymes. Oral enzyme replacement therapy is recommended for patients with symptoms of pancreatic enzyme insufficiency such as steatorrhea or weight loss.

Rash is a common adverse effect in patients undergoing treatment with EGFR inhibitors, occurring in up to 88% of patients. The rash is described as acne-like (acneiform) and appears most often on the head and upper trunk (Table 1-3). Because EGFRs are expressed on keratinocytes in the skin, inhibition of the receptor may manifest as a dry, red, itchy, papulopustular rash. The rash usually occurs a few days after the start of treatment and may wax and wane during therapy. Treatment should include emollient creams, hydrocortisone cream, or topical antibiotics such as clindamycin or erythromycin, as well as systemic antibiotics. Patients should be counseled to avoid drying agents that may worsen the rash such as benzoyl peroxide, gel-based topical antibiotics, and retinoids. Patients should also be cautioned to avoid sun exposure.

Therapy may need to be temporarily held or even discontinued if a grade 3 or 4 rash develops that is not relieved by available treatment options. Experience gained from clinical practice suggests holding the drug until the rash resolves to at least a grade 2. Once the drug is discontinued, the rash usually subsides within a couple of weeks. It may then be resumed, usually at half the dose. Because development of the rash has been correlated with efficacy in several cancers, aggressive treatment of the rash should be instituted to prevent treatment delays or discontinuation.

Future Directions

Although trials of various therapies over the last 10 to 15 years have not affected OS in pancreatic adenocarcinoma to a great extent, other agents and investigational drugs, including newer targeted therapies, continue to be studied. Research in tumor biology may expand our knowledge of risk factors and prognosis as well as identify new targets to explore. Overall survival is still the gold standard for evaluating outcomes in oncology trials. However, until new drugs and regimens are discovered that can significantly increase survival in pancreatic adenocarcinoma, QoL will continue to be an important study end point. Questions remain whether other surrogate outcomes such as response rate or PFS should be used in studies. New studies must be developed to determine the best outcome measures that will allow clinicians to establish which treatments may best fit specific patients. Future studies will also need to be designed to appropriately stratify patients into similar groupings with comparable features to decrease the diversity of patient characteristics seen within a study population.

Endocrine Tumors

An endocrine tumor is a neoplasm affecting the cells that secrete regulatory hormones. Commonly affected glands include parathyroid, adrenal, pituitary, and thyroid, as well as the endocrine pancreas and argentaffin cells. Pheochromocytomas, medullary thyroid, carcinoid, and pancreatic endocrine tumors (PETs) are further classified as neuroendocrine tumors because they arise from the neuroendocrine system. Excess hormone production from endocrine tumors can cause serious symptoms and complications.

Endocrine tumors are rare, with only about 5.25 cases per 100,000 people annually in the United States. These tumors can be found throughout the body and can be hereditary or arise sporadically. Multiple endocrine neoplasia (type 1 and type 2) are inherited disorders

Table 1-3. Acneiform Rash Severity Grading

Grade	Description
1	Papules and/or pustules covering < 10% BSA; may or may not be associated with symptoms of pruritus or tenderness
2	Papules and/or pustules covering 10% to 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL
3	Papules and/or pustules covering > 30% BSA; may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated
4	Papules and/or pustules covering any % BSA; may or may not be associated with symptoms of pruritus or tenderness; associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences

ADL = activities of daily living; BSA = body surface area; IV = intravenous.
Common Terminology Criteria for Adverse Events v4.0. U.S. Department of Health and Human Services. Published May 29, 2009. Available at *www.evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.* Accessed February 20, 2011.

associated with many of the endocrine tumors. Patients with human immunovirus infection or immune suppression because of organ transplantation also have a higher risk of these tumors.

Pancreatic Endocrine Tumors

Pancreatic endocrine tumors, also known as *islet cell tumors* or *pancreatic neuroendocrine tumors*, are subdivided based upon the type of cells that produce certain hormones. Pancreatic endocrine tumors account for only 1% of all pancreatic cancers. Although a significant number of people are diagnosed before age 35, the peak incidence occurs between ages 40 and 60. Median survival for patients presenting with local, regional, or distant disease is 136 months, 89 months, and 25 months, respectively. About half of all PETs are nonfunctional, with the rest manifesting symptoms because of excessive hormone secretion by the tumor. The latter are referred to as *functional tumors* and are seen predominantly in gastrinomas and insulinomas, although several other more rare PETs secrete excess hormones. Some of these tumors can produce several hormones simultaneously, although usually one hormone is dominant. Some PETs that are initially nonfunctional can evolve to become functional.

Clinical presentation is usually dependent on whether the tumor is functioning or nonfunctioning. The clinical manifestations of a functioning tumor depend on which hormone is being secreted. In general, patients with these tumors present with symptoms such as dyspepsia, diarrhea, weakness, dizziness, weight changes, flushing, skin rashes, jaundice, or abdominal pain. Tumors that are nonfunctioning do not typically cause these symptoms but may cause mechanical problems such as gastric or biliary obstruction. Correct imaging and diagnosis is essential. Misdiagnosis as a pancreatic adenocarcinoma, a more common disease entity with much poorer prognosis, could lead to inadequate treatment with surgery or chemotherapy.

Treatment

Optimal treatment of any PET should include surgical resection of the tumor because this is the only curative option. However, even with complete resection for patients with localized disease, it was found in one study that only 48% of patients with PET were alive and without recurrence at a median of 2.7 years from diagnosis. Surrounding lymph nodes should be tested for metastasis and any liver lesions should be resected, if possible, at the time of surgery. Symptoms of hormonal excess must be addressed before surgical resection of PETs (typically with octreotide) to prevent life-threatening hormonal surges. More than 90% of PETs express somatostatin receptors; octreotide, a somatostatin analog, inhibits hormone release and also has anti-tumor effects.

Median survival of patients with unresectable, nonmetastatic PETs is about 5 years. A clinical trial or radiation therapy for symptom control may be considered in these patients. About 60% of patients present with metastatic disease, often involving regional lymph nodes. Other sites of distant metastases may include liver, peritoneum, lung, and bones. These patients should receive chemotherapy, as should patients with tumors that cannot be completely resected. Surgical resection may be indicated for recurrent, progressive, or metastatic disease because of the clinically significant palliation and prolonged survival associated with this approach.

The role of chemotherapy for treatment of PETs is still debatable because of variations in study methodologies. For the past 30 years, studies have grouped other tumors with PETs, assessed different outcome measurements, and failed to compare chemotherapy with BSC. Streptozocin is the only drug with a U.S. Food and Drug Administration (FDA)-approved indication for use as a single agent in the treatment of PETs. Streptozocin monotherapy has an overall response rate of 36%. Two recently published phase III studies with the targeted therapies everolimus and sunitinib demonstrated increased PFS compared with placebo. Other drugs used as single-agent therapy with some success are doxorubicin, dacarbazine, temozolomide, fluorouracil, capecitabine, and interferon. Targeted agents being studied alone and in combination are bevacizumab, sorafenib, and pazopanib.

Streptozocin has been combined with fluorouracil and doxorubicin. The streptozocin-doxorubicin combination has a higher OS compared with the streptozocin and fluorouracil combination. Triple combination therapy with streptozocin, fluorouracil, and doxorubicin has been studied in two small clinical trials and in a retrospective review. Based on the response rates in these trials (29% and 55%), this triple drug regimen is considered a standard therapy for PETs. Because one of these studies showed that the response may take time to develop, the NCCN recommends treating until best response, disease progression, or treatment-limiting toxicity is seen. Chemotherapy should then be continued for an additional 4 months beyond the best clinical response in the absence of disease progression.

Other small studies have looked at temozolomide, which has the same active metabolite as dacarbazine, alone and in combination with bevacizumab, capecitabine, or thalidomide. These combinations require further study.

Insulinomas and Gastrinomas

Pancreatic endocrine tumors should be treated with surgery even when metastatic. However, treatment to control the increased secretion of hormones is dependent on the type of hormone and is usually necessary until the tumor can be resected. Gastrinomas and insulinomas make up the majority of functional PETs. Insulinomas are the most common functioning PET, although

up to 90% of these tumors are benign. Most insulinomas are found at a very early stage because of the symptoms present. Symptoms are consistent with excess insulin production and include those similar to hypoglycemia (e.g., blurred vision, palpitations, diaphoresis, tachycardia, confusion, seizure, coma). Diagnosis is through a fasting glucose study in which blood glucose and insulin levels are tested every 4–6 hours; a ratio greater than 0.4 after a prolonged fast is diagnostic for insulinoma.

Surgical management is the most common approach to the treatment of insulinomas. Careful excision of the tumor is associated with excellent long-term survival (5- and 10-year survival rates of 100% and 95%, respectively). Even when the tumor has spread to local lymph nodes or the liver, resection of accessible metastases should be considered because it can decrease hypoglycemia problems.

Controlling hypoglycemia is a critical component of treatment until the tumor can be resected, or if it is metastatic and cannot be removed with surgery. Mild symptoms may be controlled through diet, eating more frequently, and waking up in the middle of the night for a snack. In specific cases, tube feedings administered during the night may also be an option. Drugs that affect either the insulin or glucose concentrations (e.g., diazoxide, glucocorticoids, verapamil, phenytoin) may be used as pharmacologic treatment options. Diazoxide, an antihypertensive that suppresses insulin production, is the best-studied agent, providing responses in 90% to 95% of patients. Diazoxide 3–8 mg/kg/day is given in divided doses every 8 hours with dosage ranges of 50–300 mg/day. Hydrochlorothiazide is usually given with diazoxide because it potentiates the hyperglycemic effect and treats the edema secondary to diazoxide therapy. Glucagon may also be useful in some patients and is administered with a glucagon pen or as a continuous infusion. These drugs should only be used short-term because resistance eventually develops. They are most useful to maintain glycemic control until other strategies, such as surgery, are employed. Somatostatin analogs such as octreotide, which are helpful in many other PETS, should be used with caution in insulinomas because they may suppress other counter-regulatory hormones and often worsen hypoglycemia.

Treatment of insulinomas with streptozocin-based therapy is beneficial because it is toxic to insulin-producing cells and can decrease production of insulin in beta cells. It may also decrease insulin production for several years regardless of tumor response. Patients should be monitored closely if chemotherapy such as streptozocin or doxorubicin is used because the associated adverse effects such as nausea and vomiting may, in the short-term, worsen hypoglycemia.

Gastrinomas, or Zollinger-Ellison syndrome, are gastrin-secreting tumors of the pancreas. The abundance of secreted gastrin results in uncontrolled gastric acid production. About 50% of functioning PETs are gastrinomas, with most of these being malignant with a risk for metastases, most commonly seen in regional lymph nodes and the liver. Most patients with gastrinomas have a history of peptic ulcer disease, diarrhea, abdominal pain, or gastroesophageal reflux disease requiring use of acid suppressive therapy.

Serum gastrin concentrations should be obtained and assessed as part of the disease evaluation. Acid suppressive therapy must be stopped for 1 week before measurement of serum gastrin concentrations to ensure accurate results. Serum gastrin concentrations are correlated with the extent of disease: higher concentrations are present in patients with metastatic disease. Proton pump inhibitors are used to control gastric acid production. The doses used for this indication are much higher than the normal doses used for treatment of peptic ulcer disease. For example, omeprazole doses of 200 mg/day or more and lansoprazole doses of 30–120 mg/day are often necessary to control acid production. The addition of octreotide to proton pump inhibitor therapy may also be useful in some patients whose disease become refractory. Most gastrinomas are found in the early stages and are able to be resected similar to that of any nonfunctioning PET. After a complete resection, cure rates are 60% to 70%, and, in most cases, the acid suppressive therapy can be discontinued.

Further research is needed on these rare endocrine tumors to evaluate the best treatment options. Surgery remains the therapy of choice, with newer treatment targets under development. Drugs under investigation include the targeted agents sunitinib, bevacizumab, and mammalian target of rapamycin (mTOR) inhibitors such as everolimus and temsirolimus. Vaccines and peptide receptor radiotherapy are other therapies under development. As a result of the high density of somatostatin receptors on the surface of PET cells, octreotide attached to radiotherapy such as yttrium-90 may be of benefit.

Carcinoid Tumors

Carcinoid tumors are endocrine tumors that arise from argentaffin cells located in the foregut (i.e., respiratory tract, thymus, pancreas, stomach, or proximal duodenum), midgut (i.e., jejunum, ileum, appendix, Meckel diverticulum, or ascending colon), and hindgut (i.e., transverse and descending colon or rectum). About 60% arise in the midgut, with the small bowel being the most common site, followed by the appendix. About 2500 new cases of carcinoid tumor are diagnosed in the United States each year with about 50% of patients living 5 years or more after diagnosis. Patients with completely resected disease have a 20-year survival rate of 80%. However, about 80% of patients present with advanced unresectable disease. Patients with unresectable intra-abdominal disease have a median survival of 5 years. Diagnosis is through measurement of urinary 5-hydroxyindoleacetic

acid (5-HIAA) and platelet serotonin. Asymptomatic tumors are often found incidentally.

Carcinoid tumors can secrete various hormones (e.g., adrenocorticotropic hormone, gastrin, human chorionic gonadotropin, somatostatin, pancreatic polypeptide, serotonin, histamine, tachykinins). Patients with carcinoid syndrome, a constellation of symptoms associated with carcinoid tumors, describe symptoms related to the secretion of serotonin, histamine, or tachykinins into the circulatory system. Carcinoid syndrome usually does not occur unless there are metastases to the liver. The metabolic products are usually destroyed by liver enzymes before symptoms can occur. Hepatic disease results in release of metabolic products directly into the circulation through the hepatic veins and more commonly causes symptoms.

Classic symptoms of carcinoid tumors (e.g., flushing) can be triggered by alcohol, excess catecholamines, or emotional stress. Other symptoms include abdominal cramps, debilitating diarrhea caused by hypermotility, and bronchospasm accompanied by flushing caused by histamine. About 10% to 30% of patients with carcinoid syndrome also develop valvular cardiac complications with tricuspid regurgitation or pulmonary stenosis. The severity of symptoms is correlated with the concentration of urinary serotonin or its metabolite 5-HIAA and with tumor size and location in direct access to systemic circulation.

Treatment

Carcinoid tumors are categorized as locoregional or metastatic, with surgical resection performed on all localized disease. Partial liver resection is recommended if the patient is asymptomatic with a solitary liver metastasis. Surgical resection may be recommended in metastatic disease if the primary tumor is symptomatic. Metastatic disease occurs most often in the regional lymph nodes, liver, bones, and lung. Few treatment options are available if the tumor is unresectable and asymptomatic. The NCCN recommendations include observation until the disease becomes symptomatic, the use of octreotide, or enrollment in a clinical trial. Patients with metastatic disease treated with octreotide demonstrated a 67% reduction in the risk of disease progression versus placebo.

Carcinoid tumors are generally resistant to chemotherapy but often respond to radiation therapy, which is usually reserved until late in the course of advanced disease. Single-agent activity in metastatic disease has been reported with fluorouracil, doxorubicin, dacarbazine, dactinomycin, streptozocin, etoposide, carboplatin, and interferon. Response rates only range from 10% to 20% and typically last less than 6 months. Combination therapy with two or three agents has little benefit over single-agent chemotherapy, with response rates ranging from 25% to 35% and lasting less than 9 months but with increased toxity. Other agents being investigated include bevacizumab, temozolomide, sunitinib, everolimus, and capecitabine. Chemotherapy may be used in patients who are not candidates for other treatment options or eligible for a clinical trial, although it has not demonstrated any real survival benefit.

Octreotide

Octreotide is a somatostatin analog used in the treatment of patients with carcinoid syndrome. Somatostatin controls the rate of gastric emptying and regulates smooth muscle contractions, blood flow within the intestine, and neurotransmission and secretion. These effects prevent the release of growth hormone, thyroid-stimulating hormone, gastrointestinal hormones, pancreatic enzymes, and neuropeptides. Octreotide offers symptom control in greater than 80% of patients. Adverse effects of octreotide include fluid retention, nausea, glucose intolerance, cholelithiasis, and increased fecal fat excretion.

Octreotide has advantages over endogenous somatostatin, with a longer elimination half-life and binding more selectively to certain serotonin receptor subtypes. Giving octreotide subcutaneously instead of intravenously increases the half-life to 90–120 minutes with a duration of action of 8–12 hours. The NCCN panel recommends that symptomatic patients be treated with 150–250 mcg subcutaneously three times/day, with doses and frequency titrated to control symptoms. Octreotide suspended in microspheres of a slowly dissolving polymer may be used for chronic treatment. The usual monthly dosage range of octreotide suspension is 20–30 mg administered intramuscularly. One study demonstrated that octreotide suspension improved time to tumor progression compared with placebo by 1 month. This depot form may also be used in asymptomatic patients with progressing disease. Octreotide suspension suppresses 5-HIAA levels by up to 50%, and the median duration of symptomatic improvement is 1 year. Other somatostatin analogs are under investigation.

Role of the Pharmacist

Pharmacists have an important role in the treatment and care of patients with pancreatic and endocrine tumors. Much of the therapy for these diseases is focused on improvement in QoL, with strong emphasis on supportive care. Pain management, VTE prophylaxis and treatment, nausea and other gastrointestinal complaints, and nutritional issues are all areas in which the pharmacist can intervene. They can work with the patient to ameliorate adverse effects and improve the patient's QoL.

Because of the poor outcomes thus far with cancer therapy in pancreatic adenocarcinoma, continued research with new and combination therapy is needed. The pharmacist can collaborate with other medical team members to develop QoL and clinical benefit outcomes to follow in study patients. Endocrine tumors are

treated primarily with surgery, but treatment of hormonal adverse effects is necessary in functional tumors. Determining appropriate pharmacologic therapy for the excess production of hormones associated with these tumors is necessary. Symptom management, research, and treatment of these diseases are an excellent use of pharmacist knowledge and skill.

Conclusion

The treatment of tumors of the pancreas and endocrine system remains a challenge. Long-term survival in unresectable disease has not increased appreciably, especially for pancreatic adenocarcinoma. Direct comparisons of chemotherapy agents and regimens among trials are not available, and differences in trial designs and disparities in patient populations make it difficult to extrapolate benefit.

Trials have demonstrated the benefit of gemcitabine in the adjuvant treatment and for advanced pancreatic adenocarcinoma. Other chemotherapy agents are being combined in an attempt to improve response rates but with little success so far. Therapeutic options are moving from nonspecific cytotoxic chemotherapy to the promise of newer targeted therapies. The addition of erlotinib to gemcitabine was the first combination to improve outcomes in advanced pancreatic adenocarcinoma. The survival benefit, although small with this combination, brings new hope that research can capitalize on the advances made in understanding tumor biology.

Research continues to look for new signaling pathways and studies continue to evaluate novel agents. Better screening tools for the early diagnosis of disease are needed to provide the best outcomes for patients. The discovery of new tumor markers or imaging techniques that can be realistically applied to the general population will be important for the future of patients with these cancers. The hope of improved cure rates and increased survival continue to fuel the necessary research that will help attain these goals.

Annotated Bibliography

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2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: neuroendocrine tumors. v.2.2010. Available at *www.nccn.org/professionals/ physician_gls/PDF/neuroendocrine.pdf*. Accessed February 20, 2011.

   The NCCN is a nonprofit organization of 21 leading cancer centers. World-renowned experts have developed evidence-based, consensus clinical practice guidelines and recommendations for treatment of various cancers and supportive care. The guidelines are updated regularly and make recommendations in a flowchart and manuscript form that discusses the literature supporting the recommendations. The pancreatic adenocarcinoma and neuroendocrine sections of these guidelines provide a review of standard care and current research in the prevention, screening, diagnosis, treatment, and supportive management of these diseases. The guidelines discuss treatment options incorporating surgery, radiation, and systemic therapy. This is a comprehensive discussion of the many clinical trials supporting the guidelines and also includes information on future directions.

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4. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA 2008;299:1019–26.

   This randomized, controlled, phase III trial of 451 patients with node-positive disease and no prior therapy evaluated chemotherapy and radiation after complete resection. Patients were randomized to either fluorouracil (250 mg/m^2/day) or gemcitabine (1000 mg/m^2 weekly) for 3 weeks before chemoradiation and

again for 12 weeks after chemoradiation. Chemoradiation consisted of fluorouracil 250 mg/m^2/day and radiation 50.4 Gray for both groups. Crossover between groups was not allowed. For patients with tumors in the head of the pancreas, median survival was increased from 16.9 months with fluorouracil to 20.5 months in those administered gemcitabine (p=0.09). In multivariate analysis, the hazard ratio for gemcitabine was 0.80 (p=0.05). Hematologic toxicities were greater in the gemcitabine group than in those receiving fluorouracil (58% vs. 9%, p<0.001), although there were no differences in the incidence of febrile neutropenia or infection. No difference occurred between groups in the ability to complete therapy. About half of the patients in the fluorouracil arm received gemcitabine as salvage therapy upon relapse. Although this study did not demonstrate a significant difference in survival between the two treatment arms, gemcitabine with fluorouracil-based radiation has become standard when chemoradiation is considered the best therapy postoperatively.

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   This pivotal study was the first to demonstrate improved outcomes for patients with surgically unresectable advanced pancreatic adenocarcinoma. It was a randomized, single-blind study of 126 patients who had a good PS, were on stable doses of analgesics, and baseline pain intensity score of 20 or more (of 100). Gemcitabine 1000 mg/m^2/week was given for 7 weeks, then 1 week of rest, followed by weekly doses for 3 of every 4 weeks. Fluorouracil was given as a 600 mg/m^2/weekly bolus. In the gemcitabine arm, 23.8% of patients had a clinical benefit compared with 4.8% in the fluorouracil arm (p=0.0022); the median duration of clinical benefit was 18 and 13 weeks, respectively. Clinical benefit was measured by pain (assessment and analgesic consumption), functional impairment (performance status), and change in weight. Median survival was 5.65 months for the gemcitabine arm and 4.41 months for the fluorouracil arm; the probability of surviving 12 months was 18% compared with 2% in the fluorouracil arm (p=0.0025). This trial demonstrated the benefit of gemcitabine over fluorouracil monotherapy. More importantly, it supported the use of chemotherapy to improve palliation in advanced pancreatic adenocarcinoma and the design of this study methodology was appropriate to measure this outcome.

6. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960–6.

   This is the first phase III trial to show a significant advantage of combination therapy over gemcitabine alone in unresectable disease. Gemcitabine 1000 mg/m^2 was given weekly for 7 weeks, followed by a 1 week rest. Gemcitabine was then given weekly for 3 of every 4 weeks along with erlotinib 100–150 mg/day or placebo. The median OS increased for the combination therapy as compared with gemcitabine alone (6.24 vs. 5.91 months, p=0.023). Patients younger than 65 years and those with a good PS were more likely to get a drug-associated rash; having a rash was associated with a higher disease response. Median survival and 1-year survival rates, respectively, for grade 0 rash were 5.3 months and 16% and for grade 2+ rash were 10.5 months and 43%. One of the negative aspects of this study is that it is still undetermined which patient subgroups might best benefit, and questions remain about how clinically meaningful these results are.

7. Custodio A, Puente J, Sastre J, Diaz-Rubio E. Second-line therapy for advanced pancreatic cancer: a review of the literature and future directions. Cancer Treat Rev 2009;35:676–84.

   Second-line therapy for the treatment of advanced pancreatic adenocarcinoma is controversial. In this review, the authors discuss the data related to treatment of advanced pancreatic adenocarcinoma. The authors point out that no randomized controlled trials of second-line treatments have been conducted, and that studies often include different patient populations that make it difficult to draw conclusions. Their recommendations are to enroll patients in clinical trials if they have failed previous therapy and have a good PS. When data from clinical trials are not available, their recommendations are to give oxaliplatin-based chemotherapy or a combination of capecitabine with erlotinib as the standard treatment regimen. For patients with a poor PS, the authors recommend oxaliplatin, fluoropyrimidines, or paclitaxel monotherapy because these agents are fairly well-tolerated and have demonstrated improvement in symptoms. This review demonstrates the lack of good studies available so far but gives a good overview of the toxicities and efficacy seen in a large heterogenous group of patients with recurrent pancreatic adenocarcinoma.

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   This open-label study evaluated OS in 553 patients with no previous treatment who were randomized to gemcitabine alone versus gemcitabine plus capecitabine. Progression-free survival was significantly improved (5.3 vs. 3.8 months, p=0.004) for the combination therapy, but OS was not significantly different between groups. The authors also conducted a meta-analysis, described in the same publication. They combined their results with that of two other published studies. A total of 935 patients were included and a significant increase in OS (hazard ratio [HR] 0.86, p=0.02) was determined by meta-analysis, although none of the

three trials individually showed a significant improvement in OS. Quality of life questionnaires found no difference between the two groups. The authors concluded that this combination should be considered a standard option in patients with advanced and metastatic disease. However, the doses of gemcitabine and capecitabine used were very different among the three trials, and the results should be viewed with caution.

9. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer 2008;8:82.

   This meta-analysis evaluated 15 phase III trials of gemcitabine-based combination chemotherapy. The studies were categorized into three groups: gemcitabine given with platinum analogs (5 studies), in combination with fluoropyrimidines (6 studies), or with other drugs (4 studies). Gemcitabine monotherapy was the control arm in each study. Overall survival was significant in the platinum analog (HR=0.85, p=0.01) and fluoropyrimidine groups (HR 0.90, p=0.03). None of the miscellaneous agents resulted in a significant benefit in OS. A subgroup analysis of five trials with PS data found that patients with a good PS alone had significant benefit from use of combination chemotherapy (HR=0.76, p<0.001), similar to other earlier trial conclusions.

   Gemcitabine in combination with a platinum-based agent or capecitabine could be considered as reasonable in patients with advanced disease, but only in patients with a good PS. Of note, 5 of the 15 trials were only in abstract or poster form at the time of publication. Updated data were published later for one of the abstracts; no difference in OS was reported.

10. Sultana A, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. Br J Cancer 2007;96:1183–90.

    The authors attempted to perform meta-analyses on the use of radiotherapy, chemotherapy, and chemoradiation in advanced pancreatic adenocarcinoma. Eleven studies were identified of 794 patients in randomized controlled trials of patients with advanced pancreatic adenocarcinoma comparing the following therapies: (1) chemoradiotherapy followed by chemotherapy versus BSC; (2) radiotherapy versus chemoradiotherapy; (3) radiotherapy versus chemoradiotherapy followed by chemotherapy; (4) chemotherapy versus chemoradiotherapy followed by chemotherapy; and (5) fluorouracil-based chemoradiotherapy followed by chemotherapy versus another agent-based chemoradiotherapy, followed by chemotherapy. Only two of the above five planned analyses were completed because not enough studies to do the planned analysis were identified or the trials were too heterogeneous. Analysis of radiotherapy versus chemoradiotherapy, with two studies, found that chemoradiotherapy reduced the risk of death by 31% (95% confidence interval [CI]: 0.51–0.94) over radiotherapy alone. Analysis of, radiotherapy versus chemoradiotherapy followed by chemotherapy found no survival advantage with chemotherapy after chemoradiation based on two trials.

    The comparison of chemotherapy versus chemoradiotherapy followed by more chemotherapy did not demonstrate a difference in OS between the two groups, but several differences between the groups made the comparison weak. Although this was not a strong meta-analysis, it did give the impression that chemoradiotherapy is better than radiotherapy alone, which is reflected in many guidelines and treatment recommendations.

11. Anthony L, Freda PU. From somatostatin to octreotide LAR: evolution of a somatostatin analogue. Curr Med Res Opin 2009;25:2989–99.

    This review assesses the use of octreotide in acromegaly and gastroenteropancreatic neuroendocrine tumors for the past 20 years. The majority of gastroenteropancreatic neuroendocrine tumors are carcinoid tumors, for which octreotide plays a large role in treatment. Octreotide changed the way carcinoid syndrome was treated by reducing the circulating hormones and symptoms experienced by these patients, which also led to stabilization of tumor growth. One of the strengths of the article is that it goes into depth about octreotide, including its mechanism of action at various endocrine sites, its effect on the gastrointestinal tract, its pharmacokinetics and pharmacodynamics, and its adverse effects. Radiolabeled octreotide is also mentioned as a potential therapy with ongoing studies. A short section discusses treatment of chemotherapy-induced diarrhea with octreotide.

12. Rinke A, Muller H, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol 2009;27:4656–63.

    This phase IIIb study of 85 patients evaluated functioning and nonfunctioning metastatic gastroenteropancreatic neuroendocrine tumors of the midgut. Octreotide suspension 30 mg intramuscularly every 28 days given until tumor progression significantly increased time to progression for all carcinoid tumors in comparison with placebo (14.3 vs. 6 months, p=0.000072). Best responses were seen in patients with a resected primary tumor and those with a lower hepatic tumor load. At progression, many patients in the placebo group crossed over to the treatment arm. One of the weaknesses of the study is that there are no survival data yet.

    Adverse events such as diarrhea and flatulence occurred more often in the octreotide group, and five of the six patients reported to have bile stones were in the octreotide arm. Quality of life measurements were the same in both groups at study entry and at 6 months. It is known that octreotide can decrease the symptoms

associated with functioning PETs. However, one of the strengths of this study is that it is the first to look at octreotide as an anti-tumor agent. Octreotide suspension 20–30 mg was recommended for the management of recurrent or unresectable carcinoid tumors.

13. Ong SL, Garcea G, Pollard CA, Furness PN, Steward WP, Rajesh A, et al. A fuller understanding of pancreatic neuroendocrine tumours combined with aggressive management improves outcome. Pancreatology 2009;9:583–600.

    This review discusses PETs and describes the changing understanding of how these tumors have historically been categorized and the new classification system now being used. It goes into detail regarding the treatment options for these tumors (e.g., surgery, radiotherapy, chemotherapy) and also discusses future directions. A treatment algorithm is included, which is useful to better understand the complex process of diagnosis, treatment, and management of recurrent disease. This is a helpful review of the generally recognized guidelines and attitudes toward treatment of PETs because little primary literature is available to definitively support current treatment decisions.