Pancreatic cancer will account for about 6% of all cancer-related deaths in 2008. Patients often present with advanced disease, so treatment remains a challenge. This article will review the risk factors, pathology features, clinical symptoms, diagnosis and staging guidelines, treatment, and nursing implications of pancreatic cancer. This article also will review studies that have precipitated the shift in systemic treatment from 5-fluorouracil to gemcitabine. Targeted therapies will further shift treatment strategies to improve survival as more is learned about the molecular basis of pancreatic cancer.

At a Glance
- The incidence of pancreatic cancer almost equals the mortality rate.
- Pancreatic cancer has no early warning signs and symptoms, so most patients present with advanced disease.
- The backbone of treatment for pancreatic cancer has been 5-fluorouracil, but the paradigm has shifted to gemcitabine.

No clear dietary link exists between food with a high-fat content and developing pancreatic cancer, although people with increased body mass indexes are believed to be at higher risk. The role of diabetes, alcohol, and chronic pancreatitis in the development of pancreatic cancer is debatable (Coleman, 2005; NCCN, 2008). True familial pancreatic cancer is rare. However, people with a family history of hereditary nonpolyposis colorectal cancer are predisposed to developing pancreatic cancer (Yeo et al., 2005). Other genetic syndromes associated with pancreatic development include hereditary pancreatitis, hereditary breast and ovarian cancer, familial atypical multiple mole melanoma syndrome, Peutz-Jeghers syndrome, and hereditary ataxia-telangiectasia (Yeo et al.).

Pathophysiology
The pancreas is a secretory gland. Ninety percent of pancreatic cancers are ductal adenocarcinomas, which occur in the...
exocrine portion of the gland (Yeo et al., 2005). Acinar and ductal cells are the two major types of epithelium in the exocrine pancreas, where 90% of pancreatic cancers arise (Coleman, 2005). About 60%–70% of pancreatic cancers involve the head of the pancreas or the uncinate process (Coleman; Sauter & Coleman, 1999). Figure 1 demonstrates the regions of the pancreas. Ninety percent of pancreatic cancers have perineural invasion, 70% have lymphatic spread, and 50% have venous involvement at diagnosis (Coleman). Also, 20% of pancreatic cancers have invaded the duodenum at diagnosis (Coleman; Freelove & Walling, 2006; Yeo et al.).

Pancreatic tumor cells have a dense collagenous stroma with atrophic acini, preserved islet cell clusters, and a moderate increase in the number of normal and cancerous ducts. Other types of pancreatic cancers include mucinous cystadenocarcinomas, acinar cell carcinoma, islet cell tumors (originating in the Islet of Langerhans), and primary nonepithelial tumor of the pancreas (Coleman, 2005; Yeo et al., 2005). Pancreatic cancer metastasizes to the liver via the lymphatics (Mulcahy, Wahl, & Small, 2005).

Symptoms and Clinical Features

Pancreatic cancer tumors are among the most difficult to detect and diagnose because of the anatomic location of the pancreas (see Figure 2) and the insidious nature of the disease. Patients with pancreatic cancer often present with vague and nonspecific symptoms that depend on the tumor’s location and have no early warning signs. Classic symptoms include weight loss, painless jaundice, and abdominal pain. Other symptoms may include dyspepsia, nausea, vomiting, and fatigue. The weight loss experienced by patients with pancreatic cancer usually is gradual and progressive. More than two-thirds of pancreatic cancers occur in the head of the pancreas; as a result, patients usually present with jaundice caused by biliary tract obstruction. Biliary obstruction can increase levels of conjugated bilirubin and alkaline phosphatase and, as a result, the patient’s urine darkens. In addition, the stool may be pale from decreased stercobilinogen in the bowel. Malabsorption of pancreatic enzymes may cause a change in bowel habits (e.g., steatorrhea). If hepatic function worsens, patients may bruise from the loss of clotting factors (Coleman, 2005; Freelove & Walling, 2006).

Pain is the most common presenting symptom in patients with pancreatic cancer. The dull, constant abdominal pain associated with pancreatic cancer radiates to the middle of the upper back, worsens at night, and is aggravated by lying flat. The pain may become gnawing as a result of tumor invasion of the celiac and mesenteric plexus. Severe pain usually is associated with either the splanchic nerve and retroperitoneum or a lesion located in the body and tail of the pancreas. Duodenal obstruction often causes nausea and vomiting (Coleman, 2005; Freelove & Walling, 2006).

Diagnosis and Staging

Many patients with pancreatic cancer undergo seemingly healthy physical examinations. However, patients with advanced disease often have painless jaundice, hepatomegaly, ascites, splenomegaly, lymphadenopathy, a palpable abdominal mass, or abdominal fullness. Diagnosis usually is made after a mass is found on computed tomography (CT) scan. The CT scan helps surgeons to assess for resectability by identifying the relationship of the tumor to the celiac axis and superior mesenteric vessels. An endoscopic retrograde cholangiopancreatography is used to cannulate blocked ducts, and an endobiliary stent may be placed if the ducts are obstructed. In addition, biopsy and brushings can be done using this procedure to obtain a pathologic diagnosis. An endoscopic ultrasound can obtain detailed information about the lymph node status and vascular invasion of the tumor. Laparoscopy can evaluate for peritoneal studding and liver metastases not seen on CT scan. Laparoscopy also can be done for staging if metastatic disease is suspected before surgery is performed (Freelove & Walling, 2006; Yeo et al., 2005).
CA 19-9 is a tumor-associated antigen that can be a highly sensitive marker in pancreatic cancer. CA 19-9 commonly is expressed and shed in normal and diseased pancreatic tissue, and can be elevated in benign biliary and pancreatic conditions (Freelove & Walling, 2006; Yeo et al., 2005). Kim et al. (1999) found that, at a value of 37 U/ml, CA 19-9 was 76.7% sensitive and 87.1% specific in detecting pancreatic cancer. The normal CA19-9 level is less than 37 U/ml. Ferrone et al. (2006) evaluated whether perioperative CA 19-9 levels in patients with resectable pancreatic adenocarcinoma could predict stage and survival. The researchers found that lower preoperative CA 19-9 values correlated with a lower pathologic stage and better postresection survival. Ferrone et al. also noted that lower postoperative CA 19-9 levels were associated with longer survival. The postoperative CA 19-9 findings correlate with those of Montgomery et al. (1997). However, CA 19-9 should not be used to screen asymptomatic or high-risk patients.

Clinicians can make treatment recommendations using the American Joint Committee on Cancer (AJCC) guidelines, which stage a tumor based on size, lymph node status, and evidence of metastatic disease (Greene et al., 2002) (see Figure 3). The AJCC guidelines changed in 2002 to include tumor (T) classification that distinguishes between potentially resectable (T3) lesions and locally advanced, unresectable (T4) primary pancreatic tumors. The stage groupings also changed, allowing stage III pancreatic tumors to signify unresectable locally advanced pancreatic cancer, whereas stage IV is reserved for distant metastatic disease (Greene et al.).

Treatment

Surgery

Surgical resection of the tumor and surrounding tissue is the only curative therapy for pancreatic cancer. The surgical options for pancreatic cancer include classic pancreaticoduodenectomy (Whipple operation), pylorus-preserving pancreaticoduodenectomy, extended or radical pancreaticoduodenectomy, total pancreaticoduodenectomy, or distal pancreatectomy (Coleman, 2005). The type of surgical procedure used depends on the location of the tumor. The Whipple operation removes the head of the pancreas, the uncinate process, duodenum, proximal jejunum, gallbladder, common bile duct, and distal stomach, as well as anastomosis of the common hepatic duct and the remaining pancreas and stomach to the jejunum. The Whipple operation can be done for tumors located in the head, neck, and uncinate process of the pancreas (Coleman, 2005; Freelove & Walling, 2006; Yeo et al., 2005). A total pancreaticoduodenectomy may be performed if diffuse carcinoma of the entire gland or a multicentric tumor is present. A distal pancreatectomy is performed if the tumor is located in the body or tail of the pancreas (Coleman).

The NCCN (2008) guidelines defined unresectability of pancreatic cancer as distant metastatic disease, superior mesenteric artery or superior mesenteric vein involvement, celiac encasement, portal vein occlusion, inferior vena cava, or aortic encasement or invasion. Local recurrence occurs in 86% of patients with pancreatic cancer after surgery alone. Patients with locally advanced pancreatic cancer have a median survival rate of 6–10 months with surgery alone and 10–12 months with surgery fol-

lowed by chemoradiotherapy. Patients with metastatic disease have a median survival rate of three to six months with no treatment (Ko & Tempero, 2005; Mulcahy et al., 2005). Performance status and stage of disease at diagnosis are important predictors of a patient’s success with treatment.

Chemoradiation

No standard adjuvant chemotherapy exists for pancreatic cancer. In 1985, the Gastrointestinal Tumor Study Group did a prospective randomized study of 43 patients with pancreatic cancer. The patients were randomized to surgery alone or surgery followed by chemoradiotherapy. 5-fluorouracil (5-FU) was used for radiation sensitization, followed by weekly 5-FU for two years or until relapse. Patients who received combined treatment had a 20-month survival advantage and a 42%
two-year survival rate versus patients who received resection alone and had an 11-month survival advantage and two-year 15% survival rate. Although conclusions could not be drawn because of the low number of participants, the study became the basis for further research in pancreatic cancer (Kaiser & Ellenberg, 1985).

The European Study Group for Pancreatic Cancer published a randomized controlled study done in a 2 x 2 factorial design in which patients were randomly assigned to chemoradiotherapy, chemotherapy, no treatment, or both treatments after resection (Neoptolemos et al., 2004). IV bolus 5-FU chemotheraphy was given with leucovorin on five consecutive days for six cycles at 28-day intervals. The median survival in patients receiving chemoradiotherapy was 15.9 months, compared to 17.9 months in the no-chemoradiotherapy group (p = 0.0009). The median survival was 20.1 months in those who received chemotherapy alone versus 15.5 months in those who did not receive chemotherapy. The five year survival estimates were 21% and 8%, respectively (Neoptolemos et al.). Chemotherapy maintained the survival benefit despite stratification by resection margin involvement, lymph node involvement, and tumor grade and size. Patients receiving chemotherapy had a numeric survival advantage, although the difference did not reach statistical significance. No conclusive evidence shows that chemoradiotherapy improves local control; in addition, improving local control does not correlate with improved survival (Neoptolemos et al.). However, the results often are criticized because of the study design.

Adjuvant Chemotherapy

The Radiation Therapy Oncology Group conducted a phase III study which compared adjuvant 5-FU to adjuvant gemcitabine given around 5-FU-based chemoradiotherapy. The median survival was 20.6 months in the 5-FU group versus 36.9 months in the gemcitabine group. Patients with pancreatic head tumors had improved survival compared to patients with tumors in the body and tail of the pancreas (Regine et al., 2006).

In another phase III study of adjuvant pancreatic cancer treatment, gemcitabine was evaluated. An advantage in median disease-free survival was seen in the gemcitabine group (15.4 months) compared to the observation group (6.9 months) (p < 0.001) (Oettle et al., 2007).

Chemotherapy for Metastatic Pancreatic Cancer

Metastatic pancreatic cancer treatment is a challenge. The U.S. Food and Drug Administration approved the use of gemcitabine for pancreatic cancer based on a randomized phase III clinical trial (Burriss et al., 1997). In the trial, 126 previously untreated patients with advanced pancreatic cancer were randomized to receive either a weekly infusion of gemcitabine or bolus 5-FU infusions. The primary endpoint was defined as a clinical benefit response with parameters including pain intensity, analgesic use, performance, and status and weight changes. The trial showed that gemcitabine was significantly superior to bolus 5-FU with a clinical benefit response of 23.8% in the gemcitabine-treated patients versus 5% in the 5-FU-treated patients (p = 0.0022). A median survival of 5.7 months was seen in the gemcitabine-treated patients compared to 4.4 months in the 5-FU-treated patients (p = 0.0025). In addition, the one-year survival rate was 18% for gemcitabine-treated patients and 2% for 5-FU-treated patients. (Burris et al.; Ko & Tempero, 2005). As a result of the study, gemcitabine became the standard treatment in advanced pancreatic cancer. The NCCN (2008) guidelines recommended single-agent gemcitabine be given at 1,000 mg/m² over 30 minutes weekly for three weeks every 28 days.

After superiority to 5-FU, gemcitabine was evaluated in different combinations. The National Cancer Institute of Canada Clinical Trials Group conducted a phase III study from 2001–2003 of erlotinib with gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. The gemcitabine with erlotinib group showed an improvement in overall survival (p = 0.03) with a one-year survival rate of 24% versus 17% in the gemcitabine alone group. In addition, progression-free survival improved significantly in the gemcitabine with erlotinib group (p = 0.003) (Moore et al., 2007).

Rothenberg et al. (1996) conducted a single-arm phase II clinical trial evaluating gemcitabine’s effect on clinical benefit response in patients with advanced pancreatic cancer who were 5-FU refractory. Clinical benefit response was measured by pain, performance status, and weight. The study demonstrated a median survival of 3.9 months, with time to progression of 2.5 months, therefore supporting the survival benefit seen with gemcitabine (Saif, 2006).

Tempero et al. (2003) conducted a phase II study that compared intense doses of gemcitabine (2,200 mg/m²) given over 30 minutes versus fixed-dose rates of gemcitabine (1,500 mg/m² at 10 mg/m² per minute), both given on days 1, 8, and 15 every 28 days. Ninety-one percent of the patients had metastatic disease. The median survival rate for patient with metastases was 4.9 months in the intense-dose group versus 7.3 months in the fixed-dose group (p = 0.094). The researchers concluded that gemcitabine in a fixed-dose infusion warranted continued evaluation.

Another phase III study evaluated gemcitabine versus gemcitabine and oxaliplatin in patients with advanced pancreatic cancer. Gemcitabine and oxaliplatin were superior in response rate (26.8 versus 17.3%, p = 0.04), progression-free survival (5.8 months versus 3.7 months, p = 0.04) and clinical benefit (38.2% versus 26.9%, p = 0.03). A median overall survival rate of 9.0 months was observed in patients treated with gemcitabine and oxaliplatin versus 7.1 months in patients treated with gemcitabine alone (p = 0.13), revealing that gemcitabine and oxaliplatin were superior in clinical benefit but not overall survival (Louvet et al., 2005).

Heinemann, Labianca, Hinke, and Louvet (2007) performed a meta-analysis of studies in advanced pancreatic cancer treated with gemcitabine combined with a platinum agent. Heinemann et al. concluded that patients with a good performance status had greater progression-free and overall survival intervals than patients who received the combined treatment versus gemcitabine alone treatment (see Table 1).

Nursing Considerations

Patients with pancreatic cancer have unique surgical, medical, and psychosocial needs. However, few nursing articles have
addressed the care of those patients. The Whipple operation is a very complex and extensive surgery. Postoperative complications may include pancreatic fistula, delayed gastric emptying, wound infection, intra-abdominal abscess, and hemorrhage (Coleman, 2005; Sauter & Coleman, 1999). Nurses must know patients' surgical history and monitor for complications. Pancreatic fistula and delayed gastric emptying are the most serious postoperative complications (Ujiki & Talamonti, 2007). After a Whipple operation, a pancreatic fistula can develop if the anastomosis between the pancreas and jejunum does not heal properly, and pancreatic fluid can leak out and erode major blood vessels (Coleman). The incidence of this complication is 2%-24% (Ujiki & Talamonti). Signs and symptoms of a bile leak include fever, abdominal pain, and peritonitis (Riehl, 2007). Patients may have biliary stents, wound drains, or feeding tubes placed during surgery. Biliary stents allow for the free flow of bile, whereas wound drains often are placed near the anastomoses and allow nurses to assess for bile, pancreatic fluid leakage, and bleeding (Coleman; Sauter & Coleman). Other immediate postoperative care includes hemodynamic monitoring, maintaining adequate hydration, assessment of dehydration, pain management, careful monitoring of intake and output (particularly from tubes and drains), and aggressive pulmonary care (Sauter & Coleman). Endocrine function may be altered after a pancreatic resection. Endocrine functions that can be affected are the production of glucagon and the secretion of insulin. Patients need to be monitored closely, particularly those who have had a total pancreatectomy. Serum glucose should be monitored postoperatively with insulin on a sliding scale administered as needed (Coleman).

Patients with pancreatic cancer who have had surgery also can develop pancreatic insufficiency, which can lead to malabsorption and steatorrhea. Patients with pancreatic cancer may require pancreatic enzyme replacement with food consumption to assist with absorption of fats and proteins (Riehl, 2007). The weight loss experienced by patients with pancreatic cancer may be multifactorial, and patients may require enteral feedings or liquid supplementation to obtain sufficient calories and protein. Bauer, Capra, Battistutta, Davidson, and Ash (2005) evaluated compliance with nutrition supplementation in patients with unresectable pancreatic cancer. Two hundred patients received two cans (measure not specified) of a protein-energy–dense supplement with or without n-3 fatty acids daily for eight weeks. The study found significant improvements in the patients' weight regardless of supplement type. Patients in the compliant group increased their weight by 0.5 kg, whereas the noncompliant group lost 0.7 kg regardless of n-3 fatty acid inclusion (p = 0.05). In addition to liquid supplements, appetite stimulants may help. Patients with pancreatic cancer often experience nausea and vomiting as well as anorexia. Nurses should suggest small frequent meals to decrease abdominal bloating and nausea. Antiemetic and prokinetic agents may be administered before meals or throughout the day to control nausea and vomiting and improve gastric emptying (Sauter & Coleman, 1999).

Patients with pancreatic cancer also are at risk for developing gastric outlet and duodenal or bile duct obstruction. Jaundice can be treated by a percutaneous drain or stent placement by a gastroenterologist or interventional radiologist. Other complications include coagulopathies and liver failure, particularly in patients with metastatic pancreatic cancer.

Pain and depression may be the most significant issues for patients with pancreatic cancer. Pain usually can be controlled with oral opioids; however, opioid side effects include obstipation and sedation. Nerve blocks (celiac plexus blocks) can be used to treat the gnawing pain often associated with pancreatic cancer. Nerve blocks can be done under fluoroscopic or CT scan guidance and may decrease the need for oral opioids. Palliative radiation therapy also may control pain, and depression can be treated with antidepressants and anxiolytics.

### Table 1. Summary of Clinical Trials in Metastatic and Locally Advanced Cancer

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>PHASE</th>
<th>TREATMENT</th>
<th>DISEASE TYPE</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burris et al., 1997</td>
<td>III</td>
<td>Gemcitabine</td>
<td>Metastatic and locally advanced</td>
<td>5.7-month median survival (p = 0.0025), 23.8% clinical benefit response</td>
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<tr>
<td></td>
<td></td>
<td>5-fluorouracil</td>
<td></td>
<td>4.4-month median survival, 4.8% clinical benefit response</td>
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<tr>
<td>Louvet et al., 2005</td>
<td>III</td>
<td>Gemcitabine</td>
<td>Metastatic and locally advanced</td>
<td>17.3% response rate, 26.9% clinical benefit response, 7.1-month median survival (p = 0.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine and oxaliplatin</td>
<td></td>
<td>26.8% response rate (p = 0.04), 38.2% clinical benefit response, 7.1-month median survival (p = 0.13)</td>
</tr>
<tr>
<td>Moore et al., 2007</td>
<td>III</td>
<td>Erlotinib and gemcitabine</td>
<td>Metastatic and locally advanced</td>
<td>24% one-year survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td></td>
<td>17% one-year survival</td>
</tr>
<tr>
<td>Rothenberg et al., 1996</td>
<td>II</td>
<td>Gemcitabine alone</td>
<td>Metastatic</td>
<td>3.9-month median survival, 2.5-month time to progression</td>
</tr>
<tr>
<td>Tempero et al., 2003</td>
<td>II</td>
<td>Gemcitabine (dose intense)</td>
<td>Metastatic and locally advanced</td>
<td>4.9-month median survival (p = 0.094)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine (fixed dose)</td>
<td></td>
<td>7.3-month median survival (p = 0.094)</td>
</tr>
</tbody>
</table>

Note: The study by Tempero et al. (2003) evaluated the use of gemcitabine and erlotinib as a potential treatment for patients with metastatic pancreatic cancer. The study found a clinical benefit response of 24% over one year, with a median survival of 4.9 months (p = 0.094).
In addition to surgical complications, chemotherapy has side effects that must be considered and managed effectively to prevent compromising patients’ quality of life. Side effects of gemcitabine include neutropenia, thrombocytopenia, leukopenia, and anemia. Myelosuppression usually is the dose-limiting toxicity. Patients may experience mild to moderate nausea and vomiting with gemcitabine. Hemolytic uremic syndrome and heptotoxicity are rare side effects. Hemolytic uremic syndrome should be suspected if patients develop microangiopathic hemolysis, increased bilirubin levels or lactate dehydrogenase levels, reticulocytosis, and severe thrombocytopenia or evidence of renal failure. Hepatotoxicity usually is evident by transient elevations in transaminase levels (Eli Lilly and Company, 2007).

Psychological support for patients with pancreatic cancer and their families is important. Nolan et al. (2006) evaluated the spiritual issues of family members who participated in an online pancreatic cancer chat room. The site was developed to provide information on pancreatic cancer and treatment options. Many family members who posted comments sought the support of others facing the same experience. Nineteen percent of all postings addressed some aspect of spirituality, and 68% of those posting comments were women. The postings revealed that hope has many meanings. Six percent of the site’s participants returned after a loved one died, allowing the site to function as a bereavement support group. Nurses must recognize that patient information should be holistic and informative. As the disease progresses and treatment options dwindle, or if patients become too ill, patients and their families should consider hospice services. Figure 4 summarizes nursing considerations for patients with pancreatic cancer.

Future Directions

Pancreatic cancer is very difficult to treat as shown by the poor response rates to therapy. Chemotherapy has been the standard treatment for many years. As the molecular basis of pancreatic cancer is better understood and use of targeted therapies may improve patient survival. Current therapies are ineffective. However, gemcitabine has replaced 5-FU as treatment for pancreatic cancer in the adjuvant and metastatic setting. Clinical trials looking at promising new drug combinations, radiation therapy techniques, and targeted therapies may improve patient survival.

Conclusions

Pancreatic cancer treatment remains a challenge. The high mortality rate almost equals the incidence, indicating that current therapies are ineffective. However, gemcitabine has replaced 5-FU as treatment for pancreatic cancer in the adjuvant and metastatic setting. Clinical trials looking at promising new drug combinations, radiation therapy techniques, and targeted therapies may improve patient survival.

References


Figure 4. Nursing Considerations for Patients With Pancreatic Cancer

- Monitor hemodynamic level.
- Maintain hydration.
- Assess for dehydration.
- Manage pain.
- Monitor intake and output.
- Provide aggressive pulmonary care.
- Manage pancreatic enzyme insufficiency.
- Provide insulin supplementation.
- Provide nutritional supplementation.
- Assess for coagulopathies.
- Assess for depression.
- Manage treatment toxicities.
- Assess for psychological support.


