Supportive Care of the Patient With Advanced Pancreatic Cancer

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This review covers symptoms and complications in patients with late-stage pancreatic cancer, including venous thromboembolism, anorexia-cachexia, pain, and depression.

Introduction

Pancreatic cancer represents only 3% of cancer diagnoses in the United States, with an estimated 43,920 new cases diagnosed in 2012, yet it remains the fourth leading cause of cancer deaths, with an estimated 37,390 deaths in the same year. [1] Despite the availability of newer and better antineoplastic combinations, the 5-year survival rate for all stages of pancreatic cancer remains dismal at 6%. [1] Although the time before death may be limited, pancreatic cancer patients suffer an average of 11 significant symptoms directly attributable to the disease [2]; oncologists thus have a host of escalating challenges to address quickly and effectively. The daunting survival statistics for patients with advanced pancreatic cancer (APC) demand a thoughtful approach, with a prioritization of quality of life from the day of diagnosis, not just in the final days to weeks of life. This paper provides an evidence-based review of the most common and concerning symptoms and complications that occur in patients with late-stage pancreatic cancer.

Venous Thromboembolism

The incidence of venous thromboembolism (VTE) is four- to seven-fold higher in pancreatic cancer than in other common adenocarcinomas. [3] The likelihood of VTE is highest during the first 3 months after diagnosis of pancreatic cancer [4, 5]; treatment with chemotherapy further increases the risk of VTE in APC. [6] Compared to hypercoaguable patients without concurrent malignancy, cancer patients are four times more likely to develop recurrent thromboembolic complications and twice as likely to have major bleeding with anticoagulation. [7, 8] In addition to this increase in morbidity, the presence of VTE is associated strongly with higher mortality, [3, 5, 9] especially if a clot is discovered within 6 weeks of the diagnosis of pancreatic cancer. [9]

Given the significant morbidity and mortality associated with VTE in APC, investigators have evaluated the use of prophylactic low-molecular-weight heparin (LMWH) to reduce the incidence of clots. In a prospective, randomized controlled trial of 312 patients with APC, prophylactic enoxaparin was given with concurrent gemcitabine. Compared to placebo, enoxaparin reduced the number of symptomatic VTEs by 8.6% at 3 months and by 10.1% at 12 months. The LMWH was well tolerated, without any significant increase in major bleeding. [10] Another study randomized 123 patients with APC to receive gemcitabine with or without concurrent dalteparin (Fragmin) in a blinded fashion. The risk of symptomatic or incidental VTE was reduced by 85% for the first 100 days and by 58% for the median follow-up of 19.3 months. Higher rates of minor bleeding or bruising were observed in the dalteparin arm (9% vs 3%); however, the occurrence of severe hemorrhagic complications was not significant. [5] Neither study demonstrated a survival advantage with prophylactic LMWH, although the studies were insufficiently powered for this endpoint. LMWH prophylaxis may be useful for preventing serious morbidity associated with thrombosis in APC patients, particularly in the highest-risk patients. However, the current literature does not yet show improved survival with empiric therapy. The results of current and future studies to evaluate cost and quality of life will be important factors in deciding the utility of prophylaxis in an individual patient. For now, thromboprophylaxis should not be routinely prescribed outside of a clinical trial. The standard of care for patients with APC remains early initiation of LMWH after the identification of thrombus, with life-long continuation. [7, 11]
Pain

The majority of patients with APC have pain at the time of diagnosis, and appropriate analgesia is a critical longitudinal component of care. Although pain management follows the model of the World Health Organization (WHO) three-step ladder,[12] many patients with APC require a multidisciplinary approach, including consultations with interventionalists, palliative care providers, and sometimes radiation oncologists. Procedures aimed at blocking the pain signals transmitted along the celiac plexus have been shown to diminish both the need for opioids and the incidence of opioid-related adverse effects.

Celiac plexus neurolysis (CPN) can be performed surgically, percutaneously under image guidance, or endoscopically with ultrasound guidance. Partial or complete pain relief is achieved in 70% to 90% of patients who are treated with CPN.[13] If pain is prominent at presentation, the evidence supports performing CPN at the time of diagnosis, during either exploratory surgery or initial endoscopy (in the latter case, under ultrasound guidance).[13] In common clinical practice, CPN tends to be reserved for patients refractory to opioids or those suffering a disproportionate level of toxicity, such that an opioid-sparing approach is desired.[13]. However, the evidence supports earlier use of CPN. CPN decreases the average use of morphine by 40 to 80 mg per day per patient and results in significantly decreased rates of constipation. Although the duration of pain relief with initial CPN is only 2 to 3 months, this improvement makes a clinical difference to most patients with APC.[14] There are a few studies evaluating the merit of repeat CPN with recurrent pain.[15] The largest of these suggests that repeat injections provide relief in 29% of cases, with only half the durability of response compared to the first procedure.[16] Further study of the intervention in this clinical setting is needed.

Malignant Biliary Obstruction

Biliary obstruction occurs in 70% to 90% of patients with pancreatic cancer but is most commonly associated with pancreas head tumors. Biliary obstruction adversely impacts patients’ quality of life,[17,18] causing cholangitis, malabsorption, pruritus, and ultimately hepatic failure.[17,19] In most cases, symptoms resolve with relief of the obstruction, which is most easily achieved if an endoscopic biliary stent can be placed. Refractory cases may benefit from either surgical bypass or an external drain placed under percutaneous transhepatic cholangiography (PTC), although these procedures should be performed in a minority of cases and only after careful consideration of the overall medical picture.

Endoscopic stenting is technically and clinically successful in the majority of patients (88%) with extrahepatic biliary obstruction caused by pancreatic cancer.[20] This approach results in less morbidity, fewer complications, and shorter hospital stays compared to the more invasive approaches.[18,20] Occlusions occur less frequently with metallic stents than with plastic ones (31% vs 87%),[20] and even less often with those made of covered metal (3%).[21] Median patency for plastic stents is 2.5 months,[20] thereby necessitating routine stent exchanges every 3 months to prevent biliary sludging and cholangitis. Alternatively, uncovered metal stents tend to remain patent for an average of 6 months[20]; covered metallic stents maintain a 97% patency rate at 12 months.[21] Cholangitis is a life-threatening emergency and occurs in 30% of patients with biliary stents. Treatment includes immediate antibiotics with an emergent stent change to avoid sepsis or hepatic abscess formation.[18] Given concerns about immunosuppression from chemotherapy or radiation, patients expected to undergo neoadjuvant therapy do best with metallic stents to minimize the risk of life-threatening complications.[22]

When endoscopic stent placement has failed, biliary stenting by PTC is an option, although the prognosis following placement of a transhepatic stent for malignancy is markedly poor even if adequate biliary drainage is achieved.[19] In a group of patients requiring biliary drainage via PTC, almost half of whom had pancreatic cancer, significant morbidity and high complication rates (62%) were reported. An average of 2.4 procedures were required in order to achieve adequate biliary drainage, with a mean hospital stay of 42 days (range: 0–188 days). The 30-day mortality was 43%, which likely reflects the overall severity of the patients’ illness, probably the result of intrahepatic metastases.[19] Although PTC biliary drainage aims to reduce the level of systemic bilirubin, this intervention rarely improves length or quality of life[23] and only adds more complications if a patient is able to receive systemic chemotherapy. Instead, a discussion regarding overall expectations in the face of terminal hepatic dysfunction is often most appropriate.
Malignant Gastric Outlet Obstruction

Bowel compression or invasion by pancreatic cancer results in gastric outlet obstruction (GOO) and requires urgent intervention for optimal palliation of intractable vomiting. Approximately 26% of patients with pancreatic cancer develop GOO over the course of the disease.[20,24] The objectives of treatment are to relieve vomiting, reestablish oral intake if possible, and ultimately improve both the length and quality of a patient’s life.[25] A self-expanding metallic enteral stent can be used to palliate symptoms, with faster return of oral intake post-procedure compared to surgical gastroenterostomy.[24] Enteral stents result in fewer immediate complications than gastroenterostomy and are often preferred by patients.[24] There is a 15% risk of re-obstruction of the stent; nonetheless, this remains the preferred option in most patients with APC.[20,26] Palliative surgical interventions are reserved for select patients with excellent performance status, minimal burden of cancer, and a longer expected prognosis.[25] Unfortunately, prognosticating is difficult; thus, most patients undergo enteral stent placement for immediate results, with an expected stent patency of 6 months.[20]

Pancreatic Exocrine Insufficiency

Pancreatic exocrine insufficiency (PEI) occurs in 80% to 90% of patients with pancreatic cancer.[27] PEI causes nonspecific symptoms, such as abdominal cramping and maldigestion,[28] and simultaneously worsens any weight loss from cancer-related anorexia and cachexia. PEI occurs in patients after surgery, after radiation, or as a result of compression of a primary tumor left in situ. Given its high incidence in APC, diagnostic testing for PEI is not necessary. Patients should be treated empirically and followed clinically for improvement in symptoms and weight gain. Pancreatic enzyme replacement therapy is critical to relieve abdominal symptoms[28] and to reverse ongoing weight loss.[29] A starting dose of 40,000−75,000 IU pancreatic lipase should be given with meals and 20,000−25,000 IU with snacks.[28] A low pH irreversibly inactivates pancreatic lipase, so supplements should never be taken on an empty stomach. Patients can take the enzymes throughout the meal for optimal mixing with any food bolus.[29] Many patients note reduced symptoms, with less urgent stools and decreased flatulence and abdominal cramping. Clinical treatment failures are almost always the result of underdosing of replacement enzymes or patient noncompliance with timing of the medication. An increase in enzyme dose and careful re-education on the timing of medication are usually effective interventions. In addition, gastric acid suppression with either an H\textsubscript{2} blocker or a proton-pump inhibitor clearly prevents the inactivation of enzymes[28,29] and improves the efficacy of enzyme replacement therapy, resulting in superior weight gain. PEI, with its nonspecific symptoms, is poorly recognized in this population of patients. Fortunately treatment offers an opportunity to improve nutritional status and quality of life dramatically.

Cancer-Associated Anorexia-Cachexia Syndrome

Cancer-associated cachexia is observed in up to 80% of pancreatic cancer patients at the time of diagnosis.[30] The weight loss and muscle wasting result from an inappropriately accelerated catabolic rate with systemic inflammation and profound anorexia. This syndrome, called cancer-associated anorexia-cachexia syndrome (CACS), includes altered taste perception, weakness, early satiety, nausea, and a loss of appetite despite profound weight loss.[30,31] Marked protein wasting is a hallmark of CACS and results in functional impairment with decreased quality of life.[30] CACS is an independent risk factor for mortality and poor therapeutic response to antineoplastic agents regardless of cancer stage.[30] Unfortunately, death is almost inevitable when patients lose 30% of their premorbid weight.[32] In CACS, weight gain is associated with improved physical function and quality of life. Initially, patients, family, and care teams focus on oral intake with high-calorie, protein-rich foods and supplements, with mixed success. There is significant evidence that megestrol acetate improves appetite and results in modest weight gain; however, the slightly increased risk of thrombosis has limited its practical use.[33] In certain patients, parenteral nutrition may stabilize weight loss and nutritional status,[30] but this approach should only be considered after a careful discussion about prognosis, expectations, and parameters for cessation of therapy.
Promising Mechanisms Under Study in Cancer-Associated Cachexia-Anorexia Syndrome [35]

Beyond the current approach of megestrol and increased caloric intake, compounds that reverse CACS by calming inflammatory cytokines and altering catabolism are promising. In a small study, orally administered omega-3 fatty acids, specifically eicosapentaenoic acid, reversed weight loss but failed to result in a definite improvement in patient-reported quality of life.[34] Because tumor necrosis factor (TNF)-α has been identified as a mediator in CACS, preliminary clinical studies show that thalidomide attenuates weight loss significantly in patients with advanced pancreatic cancer,[32] although the drug has not been approved by the US Food and Drug Administration (FDA) for this indication. In a randomized trial in patients with gastrointestinal cancers, combined therapy with megestrol acetate, thalidomide, and olanzapine increased lean body mass and halted weight loss significantly.[35] Many promising pathways to treating CACS are under investigation; these are summarized in Table 1.[36]

Depression

General distress, depression, and anxiety are significantly more prevalent in patients with pancreatic cancer than in patients with other types of cancer.[37] The diagnosis of depression is made in 33% to 70% of pancreatic cancer patients at some point in the disease trajectory.[37-39] Feelings of sadness are a normal response to the diagnosis of pancreatic cancer; however, when depressive symptoms escalate to a magnitude and duration that fulfill criteria for major depression, treatment is essential.[38] Cancer patients with depression are more likely to display hopelessness and a desire for hastened death.[40] The incidence of suicide is 11 times higher for people with pancreatic cancer than in the general population,[39] underscoring the need to address psychological distress frequently while caring for these patients. With common underlying signaling pathways, both CACS and depression are often coincident in patients with APC, making it challenging to distinguish the neurovegetative symptoms of depression from physical deterioration due to the cancer itself.[33] For this reason, depression is likely underrecognized in this population.

The most recent sets of guidelines from prominent cancer care organizations focus the discussion on screening for “distress” in patients with cancer in order to identify those who might have or might develop clinical depression. A simple standardized screening tool provided by the National Comprehensive Cancer Network (NCCN), called the “Distress Thermometer” (DT), can aid clinicians in recognizing elevated distress.[41] The NCCN-DT does not diagnose depression but is a tool to alert oncologists that a given patient needs further discussion about current concerns, with close follow-up and probably referral to a mental health provider, chaplain, or counselor. Screening leads to earlier detection and diagnosis of true depression or anxiety disorders, so that patients can have access to appropriate treatment as early as possible.

For treatment of depression, antidepressant medications in combination with psychotherapy can be used successfully in patients with APC.[38] Selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants (TCAs), due to the anticholinergic side effects of TCAs, which complicate symptom profiles in patients receiving concurrent chemotherapy.[42] Newer antidepressants, such as venlafaxine (Effexor) and duloxetine (Cymbalta), can be considered for patients with comorbid neuropathic pain.[42] With a possible benefit within 2 weeks of starting, mirtazapine may be particularly useful for depressed cancer patients suffering from concurrent insomnia and chemotherapy-induced nausea.[43]

TABLE 2
Quality of Life Attributable to Chemotherapy

The quality of patients’ lives while receiving chemotherapy for APC is incompletely understood.[44,45] In clinical trials, a demonstrated improvement in health-related quality of life (HRQOL) cannot always be equated with tumor response or a survival benefit. In the era of patient-reported outcomes, patients expect to receive chemotherapy that will not only help them live longer but also improve the quality of the life they have left to live. Improvement in HRQOL from chemotherapy has been difficult to prove, although researchers investigating treatments for APC have tried to demonstrate relief in symptom burden since the concept of “clinical benefit” was first discussed in the literature in conjunction with gemcitabine.[46] Beyond this combined measure of pain control, weight gain, and performance status, a number of tools have been studied for use in evaluating patients’ quality of life while receiving chemotherapy.

While participating in Cancer and Leukemia Group B (CALGB) study 80303, a total of 186 patients with APC received gemcitabine-based chemotherapy and completed both the Visual Analogue Scale (VAS) and the EuroQol EQ-5D—the latter a five-question survey assessing mobility, self-care, usual activity, pain, and anxiety or depression. With patients reassessed 8 weeks into treatment, VAS scores declined with chemotherapy, reflecting a poor self-perception of health regardless of whether or not the treatment was working by objective measures. However, the authors highlight that the degree of decline was significantly worse (two times greater) for patients who had progressive disease on chemotherapy. Although there were relative improvements in pain and anxiety on the EQ-5D subscales, patients suffered declining mobility, with worsening ability to perform usual activities of daily living.[47]

Importantly, the landmark French trial comparing FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) to gemcitabine included quality-of-life measures as a secondary endpoint. Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) every 2 weeks during their participation in the study, with relatively high rates of compliance throughout the first 6 months. Sixty-six percent of patients treated with gemcitabine noted a decline in their quality of life, compared with only 31% of patients receiving FOLFIRINOX, which was a statistically significant difference. An improvement in overall global health status was reported more frequently in the FOLFIRINOX arm than in the gemcitabine arm (30.1% vs 18.5%). Improvements in fatigue and dyspnea were significantly associated with an overall response to chemotherapy in both arms. Pain, insomnia, anorexia, and constipation improved significantly on both regimens, although diarrhea was worse in the FOLFIRINOX arm during the first 2 months of treatment. The objective time until definitive deterioration of the quality of life as measured by QLQ-C30 was markedly longer in the FOLFIRINOX arm, suggesting that the decline from cancer was significantly slower with FOLFIRINOX treatment. Nonetheless, the patient-reported
quality of life failed to improve in either arm of the trial.[48]

Although no trial has yet demonstrated a true improvement in the quality of life of patients receiving chemotherapy for APC, there is evidence that chemotherapy can slow the decline in quality of life significantly. It makes sense that a patient suffering symptoms from cancer would have improvement in those symptoms with any dramatic, favorable oncologic response to chemotherapy. However, this occasionally observed clinical impact has yet to be proved in research studies measuring aggregated QOL. The well-designed study by Gourgou-Bourgade and colleagues,[48] with its high-quality patient-reported outcomes, is an example for future research. This and similar studies may help patients and clinicians make more informed decisions regarding treatment options in the future.

**Palliative Care Throughout the Cancer Journey**

The combination of unfavorable survival, complex side-effect profile, and inevitable decline in quality of life seen in APC underscores the importance of good supportive care early in the disease. Many oncologists are comfortable managing the usual symptoms associated with chemotherapy and discussing the cessation of antineoplastic therapy in favor of hospice. However, oncologists become busier every year, with growing time constraints and increasing numbers of patients. Palliative care specialists are able to work within a shared model of care and can complement the oncology team in a longitudinal fashion. Initiating early referral to palliative care allows patients to build a relationship with another provider as the disease unfolds. Late referrals can expose patients and families to a new care team during a period of crisis, risking increased anxiety and a sense of abandonment by the primary oncologist.[2]

The early utilization of palliative care consultation has been shown to lengthen survival,[49] minimize physical and emotional symptom burden,[50] and improve quality of life and patient satisfaction, while minimizing costs[50] and caregiver burden.[51,52] Early involvement of a palliative care service leads to more appropriate use of hospice and reduced utilization of futile care.[50,52] The American Society for Clinical Oncology (ASCO) has made a recommendation for “combined standard oncology care and palliative care consideration early in the course of illness for any patient with metastatic cancer and/or high symptom burden.”[52] Unfortunately, many referrals to palliative care are still made only after a patient’s physical and mental well-being begin to decline. Typically, patients report severe symptoms that went untreated prior to referral to a palliative care provider.[51]

Regarded as standard of care at the end of life, hospice remains the best way to provide excellent, focused care to the dying. However, in the United States, a review of Medicare beneficiaries with pancreatic cancer revealed that only 57% died while enrolled in a hospice program. Of patients with pancreatic cancer who did utilize hospice, only one-third were enrolled more than 4 weeks before death, so most patients missed the significant benefits that hospice can provide in the last months of life. Since the 1990s, both hospice use and aggressive care in the last month of life have increased, suggesting that a transition to comfort care comes only after a tumultuous hospitalization has failed to reverse the most recent health crisis.[53] Developing an early, ongoing relationship with a palliative care provider has been proven to make the ultimate transition to hospice easier and earlier for patients and families.[51]

**Discussions About Living and Dying**

When APC is diagnosed, most patients and families have an immediate concern about prognosis, whether or not they have the courage to ask the question directly. As oncologists, it is our ethical and legal duty to inform a patient that APC is incurable, although this and any additional news is best delivered in the setting of an empathic, thoughtful dialogue. Any discussion about survival should begin with the provider asking what kind of information the patient and family are able to hear at that visit; honoring these requests for the individual patient facilitates trust. A discussion about potential chemotherapy for APC might include relevant published survival data, but should focus on any known palliative benefit—specifically the likelihood of preventing a decline in quality of life due to symptoms of the disease. A learned skill for most physicians, effective communication improves many aspects of a patient’s care, reflected in part by improved patient satisfaction.[54]

Because patients with APC ultimately die of the disease, a basic understanding of and facility with common end-of-life concerns is critical for an oncology team aiming to provide comprehensive care. For various reasons, many oncologists do not initiate critical discussions with patients regarding preferences for the end of their life even in the therapeutic course.[51] However, it has been shown
that conversations that plan for a patient’s decline and death effectively address concerns of both patients and families.[50,51] People facing an incurable illness identify spiritual and existential distress as being as important as physical comfort. Personal control is often most important to patients, such that certain patients are prepared to tolerate pain with reduced analgesia in order to retain some control.[55] From the moment of the diagnosis of pancreatic cancer, patients are grappling with the meaning of their life, fears about dying, and how to live their remaining life well. Spiritual concerns at the end of life are independently related to quality of life.[40] Spiritual or existential suffering may manifest as intractable physical symptoms, such as pain or nausea, or as a new sense of unshakable anxiety or sadness. Unresolved emotional pain may lead to irrational expectations of care providers, or pushing for more chemotherapy “at all costs.”[40] The simple act of acknowledging a person’s spiritual distress or sense of tragedy is often therapeutic, especially if a provider shows a willingness to engage in ongoing discussions. Group psychotherapy may also help provide a sense of meaning, peace, and purpose to those with existential suffering.[40]

Many healthcare providers want patients to have a “good death,” but they should be aware that this concept is highly variable. A pooled analysis of the literature defining a “good death” found 12 common threads: being in control, being comfortable, having a sense of closure, feeling valued or recognized as an individual, having trust in care providers, recognizing that death is near, having beliefs and values honored, minimizing burdens to others, reconciliation with loved ones, accepting the appropriateness of death, being remembered once gone, and preparing the family.[56] Given the complexity and variability in what constitutes a good death, conversations to determine individual preferences in this area must start early, especially since patients and families often fear a bad death from the moment of diagnosis. Appreciating these preferences near the beginning of the journey will help clinicians know when enough is enough for an individual patient and allow patients and families to experience death with dignity.

**Conclusion**

Providing meaningful supportive care for patients with APC is complex and requires ongoing close monitoring of the physical and emotional aspects of the patient’s experience of illness. Prompt management of the many symptoms and problems associated with pancreatic cancer is essential to minimize distress and optimize quality of life for patients with this devastating disease. Recognizing end-of-life concerns and patient preferences during the dying process helps clinicians find ways to alleviate suffering for patients and families. Early conversations about death will allay concerns and guide an oncologist to recommend antineoplastic therapy based on individual patient preferences and plans.

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