Supportive Care Challenges and Management in Pancreatic Cancer

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Pancreatic cancer frequently presents at later stages, contributing to its poor prognosis. Patients often present with pain and/or jaundice once the tumor has progressed enough to obstruct or damage surrounding structures. Patients may also present with weight loss or gastrointestinal symptoms such as nausea, vomiting, or diarrhea. Symptom burden among these patients can lead to poor quality of life or functionality. Understanding and treating these symptoms can lead to improved quality of life and improved ability to tolerate cancer treatment.

Pain

Pain is an intricate symptom in pancreatic cancer patients, and its multifactorial characteristics make management challenging. In this chapter, we discuss the prevalence, pathophysiology, and different approaches to pain management in pancreatic cancer patients, including specific pharmacotherapy and non-invasive therapies.

Pain is highly prevalent in cancer patients. In health and symptom surveys from the Pancreatic Cancer Action Network, 93% of respondents cited pain as a symptom, and 83% rated the pain as moderate or severe [1]. Approximately 90% of patients cited having discussions with their doctors about their pain, yet half ended up in the emergency room with uncontrolled pain and about one-third were hospitalized for pain management [1]. Poorly managed pain has significant effects on other aspects of life. Pain has been associated with poor sleep, decreased caloric intake, and social or work-related functionality loss. Better pain control has shown to not only improvement these deficits but also shown to improve survivability [2]. Poor functionality or heavy symptom burden can preclude someone from various chemotherapy options and the potential to decrease the disease burden.

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Pathophysiology of Pain in Pancreatic Cancer

Pain in pancreatic cancer is multifactorial and complicated. There are two main mechanisms of pain in pancreatic cancer: pancreatic neuropathy and pancreatic duct obstruction [3]. Both these etiologies lead to further inflammation and worsened pain severity.

Neuropathic Pain

Nerve pain in pancreatic cancer can come from direct invasion from the cancer cells, mass effect, or cancer-driven nerve growth. Direct invasion and infiltration of the cancer cells can lead to inflammation [4], and 70% of all pancreatic tumors have been found to have malignant involvement of the sheaths around the axons [5]. Involvement can include intrapancreatic nerves or extrapancreatic nerve plexuses, i.e., celiac plexus. Mass effect or this perineural invasion can lead to an increase in inflammation and release of neurotransmitters, such as substance P and glutamate, which are possible sources of pain in this patient population [6]. Neuropathy in pancreatic cancer is associated with hypertrophy of the nerves as well [7]. Higher levels of nerve growth factor (NGF), which support the maintenance, growth, and proliferation of neurons, have been associated with increased pain intensity in pancreatic cancer [8].

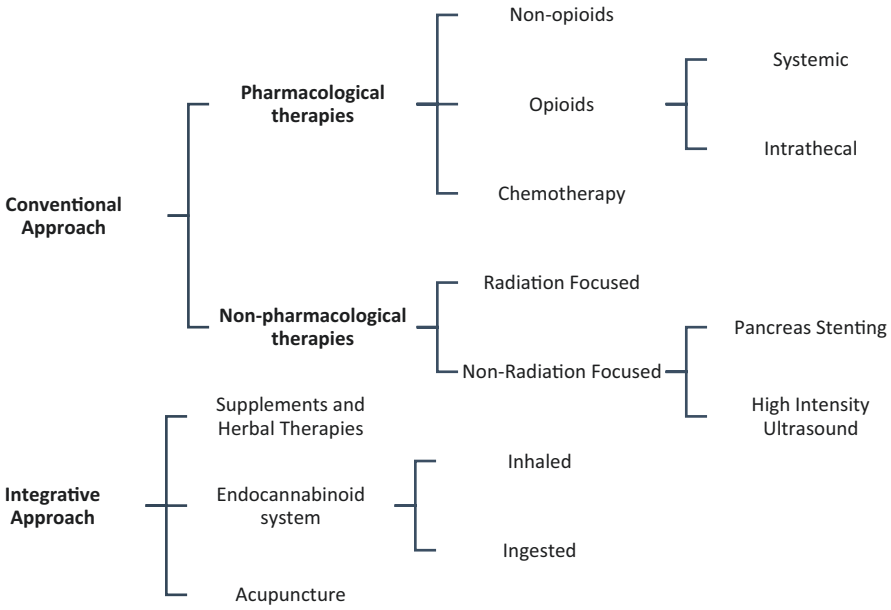
Obstruction

Pancreatic cancer mass obstructs the main pancreatic duct, leading to its blockage and pain from upstream intraductal and interstitial pressures [9]. The obstruction affects the exocrine pancreas function, decreasing the secretion of the exocrine pancreatic enzymes, and thereby, furthering abdominal pain, particularly postprandial pain, and malabsorption can occur [10]. Relief of pain has been demonstrated in studies with pancreatic ductal stenting which lowers the interstitial pressure [11, 12]. In addition, the replacement of enzymes in pancreatic insufficiency and malabsorption from other conditions have also demonstrated improvements in abdominal pain [13–15].

Pain Management

Pain management in pancreatic cancer can be broadly divided into conventional and non-conventional approaches (Table 8.1). Conventional options include pharmacological therapies such as non-opioid and opioid medications and non-pharmacological therapies such as radiation-focused and non-radiation-focused therapies. Non-conventional approaches refer to integrative therapies.

Table 8.1 Pain management approaches in pancreatic cancer



Pharmacological Therapies

Non-opioids

Nonsteroidal Anti-Inflammatory Medications and Acetaminophen

The vast majority of patients will attempt to treat pain with over-the-counter medications such as nonsteroidal anti-inflammatory medications (NSAIDs) or acetaminophen. There are more than 20 different NSAIDs produced worldwide. They work by decreasing inflammation by blocking cyclooxygenase and thereby decreasing prostaglandins, prostacyclins, and thromboxane [16]. Acetaminophen (also known as N-acetyl-p-aminophenol, APAP, or paracetamol) has an unknown mechanism of action. It may work within the central nervous system to activate serotonergic inhibitory pathways [17]. Both treat mild to moderate pain and have concerning toxicities with long-term or high dose use. There is a concern for liver damage in using high doses of acetaminophen. Its metabolites deplete glutathione and damage liver mitochondria leading to cell death. NSAIDs are associated with damage to the gastric mucosa, ulcer formation, and kidney damage.

Opioids

Opioids remain the mainstay of care for treating pain in pancreatic cancer. This class of analgesics works on the mu-receptors in central and peripheral nervous

systems. Most opioids are pure mu-receptor agonists; however, some act on other receptors. Methadone and levorphanol also exhibit N-methyl-D-aspartate receptor antagonism, and tramadol, tapentadol, methadone, and levorphanol have been shown to inhibit monoamine reuptake as well [18]. Buprenorphine is a partial mu-receptor agonist and needs further research in cancer pain [19].

The goal of opioid therapy is to maximize the functionality of patients while minimizing medication side effects. A general approach to initiating treatment is to start with an immediate release (IR) opioid on an as needed basis for moderate to severe pain. If patients require frequent dosing, they will benefit from the addition of extended-release (ER) opioids to provide more consistent plasma levels of the drug [20]. Patients are continued on their IR opioid for breakthrough pain at a dose of 10–20% of their ER medication [20].

Opioid side effects include constipation, sedation, pruritus, opioid-induced neurotoxicity (OIN), and respiratory depression. Constipation occurs secondary to increase gastric tone and decreased peristalsis and secretion. This side effect should be managed prophylactically to avoid progressive severity of symptoms such as worsening abdominal pain, nausea, and anorexia, which may already be present in patients due to their pancreatic cancer. OIN symptoms include delirium, hallucinations, sedation, cognitive impairment, myoclonus, and hyperalgesia. If present, opioids may need to be decreased or rotated to another [21]. In general, use of concomitant sedating medications such as benzodiazepines, gabapentin, or anticholinergics should be avoided to decrease the potential of OIN with opioids.

Non-medical opioid use (NMOU) is the use of prescribed opioids in ways that were not directed, such as using opioids outside of personal prescription or use of opioids for indications other than pain. Opioids are potentially abusable drugs. Recent literature suggests that approximately 20% of cancer patients exhibit some level of NMOU [22]. Universal screening for NMOU risk is recommended for all patients initiated on opioids, with periodic monitoring during the course of opioid therapy [23]. Patients need to be screened for risk factors, including personal or family history of substance abuse or mental health disorders [24, 25]. Continued monitoring for aberrant behaviors such as early refill requests, doctor shopping, urine drug screening, and inconsistent prescription drug monitoring programs data are essential [22, 23]. Patients who are at high risk for NMOU may require more frequent monitoring with shorter follow-up intervals, periodic urine drug testing, and review of prescription drug monitoring programs, and we recommend referral to pain management specialists [23]. Naloxone nasal sprays or injectables should be prescribed to patients. Their families and caregivers should be educated on signs of overdose such as excessive sedation and decreased respiratory drive and how to appropriately deliver the medication.

Intrathecal Drug Delivery

Intrathecal drug delivery systems (IDDSs) consist of a pump placed under the skin with a tunneled catheter directly into the intrathecal space by the spinal cord. The

medication used is generally an opioid analgesic, and patients can immediately note improvement in the pain. The advantage of this delivery is the reduction in pain using opioid doses that are substantially lower than what is needed with peripheral or oral administration and thus fewer side effects. Patients can have other medications added for further benefits, such as muscle relaxants or anesthetics agents. Patients can achieve significant and prolonged control of the pain. Complications are generally mild with post-procedure headaches, but patients can also get an implant infection or dehiscence of procedure wounds [26, 27].

An observational study designed to evaluate the 11-year results (2006–2017) of IDDSs for refractory pancreas cancer pain [28] demonstrated 50–75% reductions in mean pain levels [26]. In a 2002 randomized controlled trial of IDDS versus comprehensive medical management (CMM) in 146 evaluable cancer patients with refractory pain at 4 weeks, pain control was shown to be superior in the IDDS arm with fewer opioid-induced side effects [29].

Chemotherapy

Improvement of pain is a frequently studied outcome of systemic chemotherapy, and the management of pancreatic cancer can also improve both pain and patients' quality of life. Significant pain improvement has been found in studies of both first-line and second-line chemotherapy [30–32].

Non-pharmacological Therapies

Radiation Focused

Radiation therapy is a non-invasive intervention to treat tumors and has been found to reduce pain significantly. This likely improves pain by either alleviating the obstruction of the pancreatic ducts, decreasing the perineural invasion, or decreasing the tumor mass. Patients are generally treated with 6–30 Gy in 1–10 fractions. Response rates vary by fractions and study but have improved pain in 60–100% of patients [33, 34]. A strategy called stereotactic body radiation therapy can be used to limit the amount of radiation the surrounding organs receive. Due to the unique position of the pancreas in relation to other organs, the beam of radiation will meet the body at different angles to continue to treat the tumor with decreased time penetrating elsewhere and thus less damage to the other vital organs [35]. A recent systematic review has shown that between 16.5 Gy and 45 Gy in one to six fractions resulted in pain response rates of over 80%, with 54% of patients reporting complete pain resolution [36]. The study also showed a significant reduction in nausea, fatigue, weight loss, and anorexia.

Non-radiation Focused

Stenting of Pancreas

The obstruction of the ducts can also be mechanically unobstructed. Stenting of the ducts has been found to decrease pain since it will decrease both the upstream and interstitial pressures [12, 37].

High-Intensity Ultrasound

Ultrasound can be used as part of another noninvasive way to ablate and disrupt targeted tissue [38]. This procedure is being used for various solid tumors, pancreatic cancer included [39]. The heat can cause a rapid temperature increase in a small volume in tumors to induce necrosis and cavitation of the tumor. This necrosis can further damage outward to a larger volume due to mechanical damage from the cavitation pressures and gas formation. Aside from treating cancer at the tumor site, the procedure has been shown to decrease pain as well [40], likely from a decrease in mass tumor effect or possibly acting directly on nerve fibers in the tumor and celiac plexus.

Neurolytic Procedures

Patients can also have improved pain from neurolytic procedures that involve application of chemical agents to result in a permanent or temporary degeneration of targeted nerve fibers to interrupt neuronal transmission. Celiac plexus neurolysis (CPN) and thoracoscopic splanchnicectomy (TS) are invasive neurolytic procedures that may improve pain and/or decrease the need for opioids in managing pain related to an upper abdominal malignancy, such as pancreatic cancer. Recent studies support the use and efficacy of neurolytic procedures early in the management of pain, such as after one or two trials of opioid therapy have been inadequate for pain control. The neurolytic injectate is usually 50–100% ethyl alcohol. For CPN, several techniques may be used to approach the celiac plexus, such as percutaneous (aided by fluoroscopy or computed tomographic imaging), surgical placement, or endoscopic ultrasound. Several CPN studies have demonstrated significant improvements in pain at 2, 4, or 8 weeks [41, 42], and in some studies, this was associated with lower opioid usage [43]. The 2011 Cochrane review (six RCTs, published 1993–2008) [44] demonstrated significantly lower pain scores at 4 weeks (−0.43; 95% confidence interval [CI], −0.73, −0.14; $p = 0.004$], with a trend toward lower pain at 8 weeks (−0.44; 95% CI, −0.89, −0.23; $p = 0.06$]. In subsequent reviews by Nagels et al. (2013, five RCTs) and Zhong et al. (2014, eight RCTs), statistical improvements in pain scores with CPN were found at 4 but not at 8 weeks [45, 46]. Thus, current evidence suggests that percutaneous CPN improves pain scores at 4 weeks, which may not be sustained over time. However, all three meta-analyses demonstrated significant reductions in opioid consumption at 4 and 8 weeks or last report.

Integrative Therapies

A substantial number of patients with pancreatic cancer do not achieve satisfactory relief with first-line pharmacotherapy and noninvasive second-line therapies. This common scenario may be addressed in many ways with the following non-conventional therapies.

Supplementation and Herbal Therapies

Patients commonly supplement their prescribed medical therapies with over-the-counter herbal remedies [47]. Many of these herbal medicines or nutraceuticals lack evidence-based support for significant improvement of pain or other symptoms. Some have been shown to cause organ damage or interact with medications or chemotherapy by increasing toxicities or decreasing efficacy [48, 49]. The safest recommendation for patients is thus to discontinue use while receiving treatment.

Cannabinoids

Cannabinoids act on central and peripheral nervous systems. Receptors have been found to act on the gastrointestinal tract, immune system, and more directly nerves and the brain [50, 51]. Endocannabinoids, endogenous cannabinoids, affect metabolism through these receptors. The drug has historically been inhaled or orally ingested.

Medical marijuana has been becoming increasingly available to patients. As of 2022, 37 states allow the legal use of medical marijuana. Cannabis has been touted as treating diverse problems, including pain, nausea, loss of appetite, inflammation, poor mood, and even seizures [52]. There are synthetic forms of THC that have been approved to treat nausea and vomiting, but limited data support its use in analgesia.

Acupuncture

Acupuncture is a nonpharmacologic intervention consisting of small, thin needles placed in specific areas known as "meridian points" that are thought to more specifically affect neurotransmitter release [53]. Data has been mixed; studies that show significant pain relief have shown the onset of analgesia after about a day and can last for day*s* [54]. Patients interested in this intervention should be referred to the appropriate specialist.

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