ANTICANCER RESEARCH *40*: 1789-1796 (2020)
doi:10.21873/anticanres.14133

Review

Pathogenesis and Treatment of Pancreatic Cancer Related Pain

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Abstract. *Pancreatic cancer is often diagnosed due to the patient seeking medical attention for abdominal pain. It is among the most painful cancers, with pain severity strongly correlating with prognosis. Perineural invasion is a prominent feature of pancreatic cancer and often the first route of metastasis resulting in neuropathic pain. While surgical pain is present, it is generally short-lived; chemo- and radio-therapy associated side effect pain is often longer lasting and more difficult to manage. Treatment-induced mucositis in response to chemotherapy occurs throughout the GI tract resulting in infection-prone ulcers on the lip, buccal mucosa, palate or tongue. Cisplatin treatment is associated with axonal neuropathy in the dorsal root ganglion, although other large sensory fibers can be affected. Opioid-induced hyperalgesia can also emerge in patients. Along with traditional means to address pain, neurolytic celiac plexus block of afferent nociceptive fibers has been reported to be effective in 74% of patients. Moreover, as cancer treatments become more effective and result in improved survival, treatment-related side effects become more prevalent. Here, pancreatic cancer and treatment associated pain are reviewed along with current treatment strategies. Potential future therapeutic strategies to target the pathophysiology underlying pancreatic cancer and pain induction are also presented.*

Pancreatic cancer is the 2nd most common cause of cancer-related death, despite only being the 20th most common cancer diagnosis. With the highest mortality rate among all major cancers, 5-year survival rates (Stage I~13%, Stage II~6% , Stage III~3%, Stage IV~2%) have not improved significantly over the past decade (1-3), even though extensive research efforts have uncovered new risk factors (4-9), genetic mutations (8, 10-18) and therapeutic options (19-26). Pancreatic cancer is generally a disease of older patients that is characterized by late diagnosis, rapid disease progression and resistance to chemotherapeutic treatments (1, 3). Often called the "silent killer", pancreatic cancer shows few to no symptoms in the early stages. When symptoms, specifically pain, are perceived by the patient they are vague and nonspecific often leading to late diagnosis and poor prognosis due to metastasis to surrounding organs (27-30). Studies have shown that the majority of pancreatic cancer patients, around 75%, present with pain at the time of diagnosis although pain intensity varies depending on the site of distribution in the pancreas, anatomy and the presence of metastatic lesions or local invasion (28-32). Pain management is especially challenging, due to advanced patient age, the aggressive nature of the disease and the use of aggressive treatment regimen. Interestingly, the presence and severity of pain in pancreatic cancer patients correlates strongly with pancreatic cancer prognosis and an adverse tumor microenvironment, suggesting that a more toxic cancer environment correlates with increased nerve damage (29, 33-39).

Currently available pancreatic cancer treatments often exacerbate pain, and pain management strategies are almost exclusively opioid in nature, which not only have significant side effects, but do little to address the underlying causes. There is a specific, urgent need for better treatments for pain in pancreatic cancer patients.

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Key Words: Pancreatic cancer, pain, cancer treatment-induced pain, pancreatic cancer treatment, pancreatic cancer pain.

Pancreatic Cancer-induced Pain

Pancreatic cancer patients typically suffer from high levels of abdominal pain symptoms that arise from a variety of causes including tissue damage, inflammation, ductal obstruction and infiltration, and can be visceral, somatic or neuropathic in origin (28-33).

Somatic pain arises from local invasion and metastasis into the surrounding peritoneum, retroperitoneum, and bones, while visceral pain arises from the infiltration of adjacent organs, such as the liver and the accumulation of ascites in late stage patients (28-31). Specifically, pain resulting from metastasis to the liver and bile duct present problems due to high incidence rates in pancreatic cancer patients. Somatic pain signals are transmitted by the celiac plexus nerves (T12-L1) via the sympathetic system through the splanchnic nerves (T5-T12) and to the central nervous system (40). Visceral pain is caused by damage to the upper abdominal viscera (28, 41). Nociceptive signals are carried along sympathetic fibers to the celiac plexus nerves and ganglia (T12-L2) and are transmitted through the splanchnic nerves (T5-T12) and to the higher centers of the central nervous system (40).

Perineural invasion is a prominent feature of pancreatic cancer and often the first route of metastasis (28, 31, 33, 41-43). Extra-pancreatic nerve plexus invasion is responsible for the neuropathic pain sensation. Similarities in growth factor receptors and adhesion molecules between pancreatic cancer cells and neuronal cells, explain the affinity to neural tissue and lead to increased cancer cell proliferation, and migration and invasion along nerve bundles. Pancreatic cancer cell migration along nerve bundles results in neuropathic pain, increased neuroplasticity and pain sensation in response to growth stimulation of sensory fibers (34).

Treatment-induced Pain

Pancreatic cancer patients receive a number of invasive interventions as part of the cancer diagnosis and curative/palliative treatment approaches (1, 3), either as part of standard-of-care or as part of clinical trials. Novel therapeutic approaches or combination treatments are continuously evaluated pre-clinically and clinically in an effort to replace current treatment-induced toxicities (37, 38, 44-51). Although the pain inflicted by cancer surgery or diagnostic procedures can be intense, these pain symptoms are generally short-lived and can be easily addressed pharmacologically in most cases (32, 52). Systemic side effects from treatment with chemotherapy, radiotherapy of the combination, such as bone marrow suppression, immunosuppression, nausea, vomiting, diarrhea, fever, anorexia, asthenia, cachexia, cardiovascular, renal and hepatic toxicity, alopecia, sloughing of skin and mucosal membranes, as well as central and peripheral neuropathic toxicities, however, can persist throughout the treatment and are not easily addressed without treatment interruption (52-55).

Cancer treatments have become significantly more effective over the last decade resulting in longer patient survival, which also makes treatment-related side effects more prevalent. Specifically, peripheral neuropathic pain and mucositis are common and very painful side effects of a number of chemotherapeutics (cisplatin, fluorouracil, neurotoxic chemotherapy) and radiation and can be dose-limiting (52-57).

In pancreatic cancer, treatment-induced mucositis is common in response to treatment with standard-of-care (cisplatin, 5-FU, taxanes), and occurs throughout the GI tract (esophagus, small and large intestine) (56, 58-60). The most prominent symptoms are observed in the oral mucosa with ulcers on the lip, buccal mucosa, palate or tongue. The initial inflammation is followed by secondary bacterial, yeast (thrush) and/or viral infections. Initial symptoms often manifest toward the end or after completion of the treatment cycle and can persist for weeks depending on the treatment regimen (53, 54, 59, 61). Additional side effects are malnutrition and weight loss.

Chemotherapy-induced neuropathic pain is commonly observed in cancer patients in response to a variety of chemotherapeutic drugs (52, 55, 59, 62). In pancreatic cancer specifically, cisplatin treatment is associated with axonal neuropathy in the dorsal root ganglion, although other large sensory fibers can be affected. Similar results have been observed in response to treatment with oxaliplatin (55, 63, 64). Gemcitabine and taxanes are also associated with a spectrum of neuropathies. Gemcitabine-induced neuropathies range from mild paresthesia to severe peripheral and autonomic neuropathy (55, 62, 64). Taxanes induce neuropathic symptoms such as peripheral burning-like sensations and numbness, paclitaxel-associated acute pain syndrome, motor neuropathies and autonomic neuropathy. These symptoms are dose-dependent and must be weighed against the potential for therapeutic benefit. Most patients receive combinations of these drugs as part of their anti-cancer therapy, which can lead to synergistic neurotoxicity (55, 62).

Because pancreatic cancer patients display high levels of cancer-associated pain prior to therapy, treatment-related pain is often difficult to distinguish and may make a relatively minor contribution to the overall pain (30).

Current Clinical Pain Management

The majority of pancreatic cancer patients present with moderate to severe pain at the time of diagnosis, making pain management a priority in patient treatment (32, 65, 66). Due to the aggressive nature of pancreatic cancer, however, increasing levels of pain can be challenging to address. Pancreatic cancer-related pain is typically addressed pharmaceutically using analgesics, opioids and anti-inflammatory drugs, each of which can be associated with severe side effects (67-69). Nevertheless, the majority of cancer pain and treatment-induced pain can be addressed using the three-tier WHO analgesic ladder where mild analgesics are prioritized unless they are unable to address

the pain state, followed by progressively stronger agents and combinations (32, 66, 70). The first line treatment for pancreatic cancer pain is usually a mid-tier opioid-based pharmacotherapy aiming to control pain symptoms while minimizing opioid side-effects (71, 72). Nevertheless, individual pain and opioid tolerance require patient-specific drug selection, consideration of route, individualization of the dose and common side effect management. Adjuvant analgesics, such as glucocorticoids, antidepressants and anticonvulsants, can be helpful when opioid treatment alone is not successful.

Opioid-induced hyperalgesia (OIH) can emerge in patients, and is likely to increase in prevalence alongside successful cancer treatment. OIH is a condition in which the opioid therapy prescribed to relieve pain results in a paradoxical worsening of the pain symptoms (73). CNS adaptation to opiates can result in hyper-sensitization to pain signals, especially when opiates are discontinued (74). Opiates can also induce inflammation, which can exacerbate pain and contribute to OIH. While discontinuing the opioid or providing mu opioid receptor antagonists are treatment options, this is not always possible in pancreatic cancer patients. In this case, opioid reduction or a switch to buprenorphine or a different structural class of opioids is warranted.

Surgeries removing the tumor (Whipple surgery, distal or total pancreatectomy) can alleviate tumor-induced pain while increasing patient survival (26). Unfortunately, only~20% of all patients qualify for surgery at the time of diagnosis (25, 35). In cases of locally advanced tumors presenting with pain symptoms associated with blockage of the small intestine or bile accumulation, biliary or gastric bypass surgery are used to reduce pain symptoms (35).

Neurolytic celiac plexus block (NCPB) of afferent nociceptive fibers as a means to relieve visceral cancer-related pain using ethanol has been reported to be effective in 74% of patients. CPB can also result in reduced need for opiate analgesics (27, 75-79). However, this method has some undesirable side effects such as induction of back pain and orthostatic hypertension (75, 76). Less frequent, though more serious, other side effects can also occur such as spinal cord injury due to spinal ischemia, among others.

A study conducted by Wong et al. analyzed the effect the neurolytic celiac plexus block (NCPB) and opioids alone, on pain relief, quality of life and survival rate in patients with inoperable pancreatic cancer (80). Results show that both treatments improve quality of life and pain intensity within the first week of administration, however, a larger decrease in pain has been observed for the NCPB group, improving their quality of life. Nerve block treatment is preferred when opioid medication results in unmanageable side effects and high pain levels. Additionally, NPCB increased 1-year survival compared to the opioids alone (16% *vs.* 6%). Overall survival, however, was not affected by either method (80). The combination of CPB and pancreas cryoablation (PCA) has been shown to effectively alleviate cancer pain for more than 8 weeks without severe side effects (81).

Cannabinoids, such as dronabinol and nabilone, are approved drugs for the symptomatic treatment of cancer-related side effects (82). Cannabinoids reduce pain symptoms through supraspinal, spinal, and peripheral modes of action and can be used to alleviate both caner- and treatment-induced pain states (63, 83, 84). Additionally, cannabinoid treatment can address the cause of pain by reducing the release of inflammatory signals and increasing endogenous opioid release through the CB2 receptors, affecting mast cell receptors and keratinocytes (83, 84). CB1 receptor is the nervous system target of cannabinoids and is found in both the central nervous system (CNS) and in peripheral nerve terminals, and high receptor concentrations in brain regions regulate nociceptive processing (83, 84). Clinically, cannabinoids are mainly used as supportive therapy to reduce pain, improve sleep and the nutritional state of pancreatic cancer patients (85).

Other treatments involve electro-acupuncture or hypnosis (86-89). Although treatment outcome and pain relief differ dramatically between patients, positive results have been observed in some patients (88). Additional follow-up of these results is required before broad implementation and replacement of more proven methods, however, given the complete lack of adverse side effects, these can be considered as adjuvant therapies without significant potential for causing harm.

Future Outlook

Pain, whether neuropathic, inflammatory or visceral in nature, results in a large number of molecular and cellular adaptations in the affected tissue and nervous system, all of which contribute to the development of chronic pain symptoms. A number of studies have provided evidence that tissue damage, as found in cancer patients, induces significant changes in chromatin structure leading to changes in local gene expression and neve function (90-92). These epigenetic changes may contribute to the development of several pain symptoms and the manifestation of chronic pain. In addition to providing a valuable insight into the molecular mechanisms of pain development and chronic pain syndromes, some studies have provided evidence regarding the use of epigenetic modulation as a potential therapeutic option for cancer-related pain (91, 93, 94).

Epigenetic enzymes such as histone acetylases (HATs) and histone deacetylases (HDACs) are fundamental regulators of gene expression that act by regulating chromatin conformation through changes in the acetylation status of histone proteins. Cancer treatment has been the primary target of HDAC inhibitor development due to their ability to reduce tumor

Table I. *Pain treatments in pancreatic cancer*

Treatment approaches	Medications and modalities	Administration route/techniques	Indications
Pharmaceutical	Opioids and derivates	Oral	Moderate to severe pain
		Subcutaneous	Impossible oral intake (occlusion)
		Patch (fentanyl)	Breakthrough pain
		Nasal	Breakthrough pain
	Antiepileptics	Oral	Neuropathic pain
	Corticosteroids	Oral or IV	Adjuvant (metastatic bone pain)
Interventional	Celiac plexus block (LA) or neuolysis	Transcutaneous guidance[1] or endoscopic ultrasonography	Refractory pain
	Splanchnicectomy	Thoracotomy, Thoracoscopy	Intractable pain
	Intrathecal therapy	Implantable intrathecal drug delivery systems	Palliative
Alternative medicine	Acupuncture	Jiaji points	Adjuvant, interventional
	Hypnosis	Hypnosis expert	Any stage of pain

[1]Ultrasound, X-ray fluoroscopy or computed tomography; IV: intravenous.

growth. Nevertheless, recent studies have shown that HDAC inhibitors can reduce inflammatory and neuropathic pain in nociceptive animal models and models of traumatic and drug-induced peripheral neuropathy (92, 95). HDAC inhibitors selective for class I and II HDAC enzymes delayed the onset and reduced pain behavior, formalin-induced inflammation and stress-induced visceral nociception (92). Chronic pain is induced by dysregulation of GABA-mediated antinociception and is associated with hypoacetylation and decreased expression of glutamate decarboxylase 2. GABA-mediated synaptic function was restored in response to treatment with HDAC inhibitors, resulting in a reduction in neuropathic pain and mechanical hyperalgesia (92).

Conclusion

Pancreatic cancer is notable for its late diagnosis, poor prognosis and debilitating abdominal and back pain. Clinical pain management remains challenging, specifically in the light of the aggressive therapeutic interventions used in pancreatic cancer treatment that further add to the cancer-induced pain symptoms. While a number of pharmacological and interventional treatment options exist for pancreatic cancer patients, the absence of specific treatment guidelines and side effects associated with available treatments limit pain management options for effective pancreatic cancer pain treatment (Table I). Recent studies have implicated modifications of the epigenome in the development of acute pain symptoms and chronic pain conditions and suggested that epigenetic modulation may provide a novel route for pain management in pancreatic cancer.

Conflicts of Interest

The Authors have no conflict of interest to report regarding this study.

Author's Contributions

IL and SPB both contributed to the writing of the manuscript.

Acknowledgements

This work is dedicated to the memory of Michael Leitl, Ph.D.

Funding

SPB receives support from the National Institutes of Health (R01NS092671 and R01MH110441), the University of Miami Sylvester Comprehensive Cancer Center Molecular Therapeutics Shared Resource (MTSR), the Jay Weiss Institute for Health Equity and the Ryan Foundation.

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Received January 16, 2020
Revised February 18, 2020
Accepted February 19, 2020