Narrative Review

Pancreatic Cancer Related Pain: Review of Pathophysiology and Intrathecal Drug Delivery Systems for Pain Management

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Background: Pancreatic cancer (PC) is one of the most lethal cancers and is the eleventh most common cancer worldwide. This disease is characterized by an often-fatal evolution and a high burden of symptoms, particularly pain. Several studies have demonstrated that pancreatic cancer patients have a high prevalence of pain, with up to 82% of patients reporting pain, often requiring systemic strong opioids as mainstay treatment. This comprehensive review of pancreatic cancer related pain (PCRP), focuses on current mechanisms that lead to pain including regional invasion processes, as well as the local secretion of factors that sensitize nociceptive nerves.

Objective: Our objective was to conduct a review of PCRP and provide updates on intrathecal drug delivery in PC therapeutic recommendations.

Study Design: We used a narrative review design. We present a novel perspective in the field of pain research by converging data from intrathecal drug delivery trials with previous elements of molecular pain research in PCRP.

Methods: The literature review relating to PCRP pathophysiology and intrathecal drug delivery systems (IDDS) was done with searches of English, French, and Spanish abstracts, using PubMed, Dynamed, EMBASE, SciELO, Uptodate, Google Scholar, and manual searches of the bibliographies of known primary and review articles from IDDS inception until August 2020. Different search strings based on MESH terms were used including: pain, chronic pain, cancer pain, prevalence, pathophysiology, pancreatic cancer, analgesia, invasive pain procedures, celiac plexus neurolysis, pancreatic neuropathy, intrathecal drug delivery, or a combination of these terms. A narrative review based on these sources was prepared.

Results: This paper reviews aspects related to pancreatic adenocarcinoma and PCRP prevalence and focuses on recent developments in pathophysiology with IDDS as a pain management strategy. We summarize the best available evidence regarding intrathecal therapy (IT) for PCRP management; 18 studies of IDDS including at least 236 PC patients are analyzed.

Limitations: Some limitations include: IDDS studies heterogeneity regarding disease stage, patient population, and technical aspects, such as catheter placement and treatment regimen, do not allow integration of studies.

Conclusion: This review analyzes both past and current literature with a critical analysis of findings and respective recommendations. Most studies of IDDS in PCRP evaluate outcomes on pain using one-dimensional pain scales, such as VAS. Other relevant results, such as performance status or quality of life, are not frequently reported. Burden of disease variables, such as cancer stage, location, and comorbidities, like depression and systemic analgesia co-prescription, are usually not presented in these studies. In the same way, most studies do not precisely inform IDDS titration and IT medication. These factors make integration of IDDS in PC studies difficult. Future studies regarding impact of IDDS on pain control on quality of life, in this particular population, may help clinicians in deciding the optimal time and approach for IDDS. The studies should report data on particular disease, comorbidities, and treatment regimens.

Key words: Adenocarcinoma, cancer pain, pain, pancreatic carcinoma, pancreatic neoplasms, pain management, physiopathology, prevalence

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Pancreatic cancer related pain (PCRP) is a distinct clinical condition characterized by presence of pain in the upper abdominal region, spreading posteriorly and/or radiating to the back, in patients with pancreatic cancer (1). This common, debilitating symptom negatively impacts patients' quality of life and leads to increased healthcare costs; moreover, PCRP correlates with negative survival outcomes, contributes to a decline in patients' functional status, and can adversely influence access to disease modifying treatment. PCRP is a highly complex syndrome that requires multidisciplinary management, frequently requiring interventional pain management on behalf of the patient.

This paper reviews aspects related to pancreatic adenocarcinoma and PCRP including prevalence and pathophysiology, with a focus on intrathecal drug delivery systems (IDDS) as a pain management strategy. The literature research was developed in English, French, and Spanish from the inception of IDDS to August 2020, using PubMed, Dynamed, EMBASE, SciELO, Uptodate, and Google Scholar. Different search strings based on MESH terms were used including: pain, chronic pain, prevalence, pathophysiology, pancreatic cancer, analgesia, invasive pain procedures, celiac plexus neurolysis, pancreatic neuropathy, intrathecal drug delivery, and a combination of the previously mentioned terms and phrases.

Epidemiology of PC

PC is one of the most lethal cancers and is the eleventh most common cancer worldwide. PC is the fourth leading cause of cancer-related death in Europe and the United States of America (2-5). Despite increasing diagnostic and therapeutic efforts, PC remains lethal and common among cancer types, with a 95% mortality/incidence ratio (6). Even with therapeutic advances in the last decade, the overall survival rate remains poor for metastatic PC. Median survival time of patients with PC in Europe was 4.6 months and less than 10% of patients survived beyond 5 years from diagnosis (7,8).

This dismal survival rate is partially attributed to a delay in diagnosis, given current limitations in disease screening and nonspecific early symptoms. Most patients with early stage PC are often asymptomatic or present with vague symptoms, such as jaundice, fatigue, decreased appetite, change in bowel habits, weight loss, abdominal pain, and mood disturbances (9,10). These unspecific symptoms may delay exhaustive clinical evaluation and lead to late diagnosis in an advanced stage case, when local or distant progression has occurred. Unfortunately, this is a common clinical scenario, thus, limiting curative treatment options (11,12).

Pain Prevalence

Pain has a high prevalence in patients with cancer, depending on disease stage and specific histology. A meta-analysis of 117 studies (n = 63,533) reported a 55% pain prevalence rate during anticancer treatment and a 66% rate in advanced, metastatic, or terminal disease. Several studies have demonstrated that amongst cancer patients, pancreatic cancer patients have a high prevalence of pain (13,14). Published pain prevalence data on PCRP show varying rates from 47% to 63% at diagnosis (15,16); this rate increases to 82% of advanced cancer patients referred to a palliative care service in a tertiary care pain facility (17). These dismal numbers negatively impact cancer patients' quality of life (18). Preclinical and clinical data suggest a positive correlation between disease progression and PCRP development (19,20). Moreover, correlation between severe pain phenotype and lower survival in PC, and between higher systemic opioids and probability of early death, has been demonstrated, suggesting severe pain is a clinical indicator of poor outcomes (21,22).

Pain Mechanisms

Pancreatic extrinsic innervation consists of sympathetic afferents derived from splanchnic nerves (greater, lesser, and least) and parasympathetic afferents derived from vagal nerves. This extrapancreatic innervation organizes in a dense web of fibers forming several regional plexi (anterior hepatic, posterior hepatic, superior mesenteric, splenic, and celiac) (23). Primary afferents innervating the pancreas connect mainly to the celiac and mesenteric ganglia. Nociceptive signals are then transmitted from the dorsal root ganglia to the spinal dorsal horns, primarily located at the T5–L1 segments (24,25).

Pancreatic nociceptive signals ascend from the viscera via the spinal cord. Classically, the spinothalamic tract has been described as the primary ascending nociceptive pathway, located in the ventrolateral white matter of the spinal cord (26); nonetheless, preclinical and clinical evidence has confirmed that visceral nociceptive signals are also transmitted through the dorsal columns via the post-synaptic dorsal column pathway (27-29). Recently, important interaction between these 2 pathways has been proven by the existence of bilat-

eral neurons and bifurcated cells interconnecting both pathways (30).

Animal studies have proven that excitatory effects, induced by application of bradykinin to the pancreas, can be abolished completely by a restricted dorsal column lesion (27). These experiments have suggested that ascending visceral input from thoracic levels travels more laterally at the dorsal intermediate septum, while input arising from sacral levels ascends in the midline of the spinal cord (31). These signals reach neurons primarily located in the ventral posterolateral thalamic nucleus and are subsequently integrated through projections in various rostral regions, such as the primary and secondary somatosensory cortex, the insula, orbitofrontal cortex, dorsolateral prefrontal cortex, amygdala, and cingulate(32). Multilateral interactions between these higher centers organize to form a network (33).

PCRP is a complex condition and several pathophysiological mechanisms have been proposed. These may be variably involved in specific cases and will be further discussed ahead, including pancreatic neuropathy, altered cortical processing, perineural invasion, intraductal pressure, bowel obstruction, and distant progression (Fig. 1).

Anatomical Factors

Tumor location seems to play a major role in PRCP development, since patients with tumors located in the pancreatic body or tail tend to have more pain than patients with cancer in the head of the pancreas, independent of tumor stage or size (15,20). Autonomic plexus invasion is often cited as a predominant pathophysiological mechanism in PCRP, occurring mainly through regional progression and macroscopic retro-

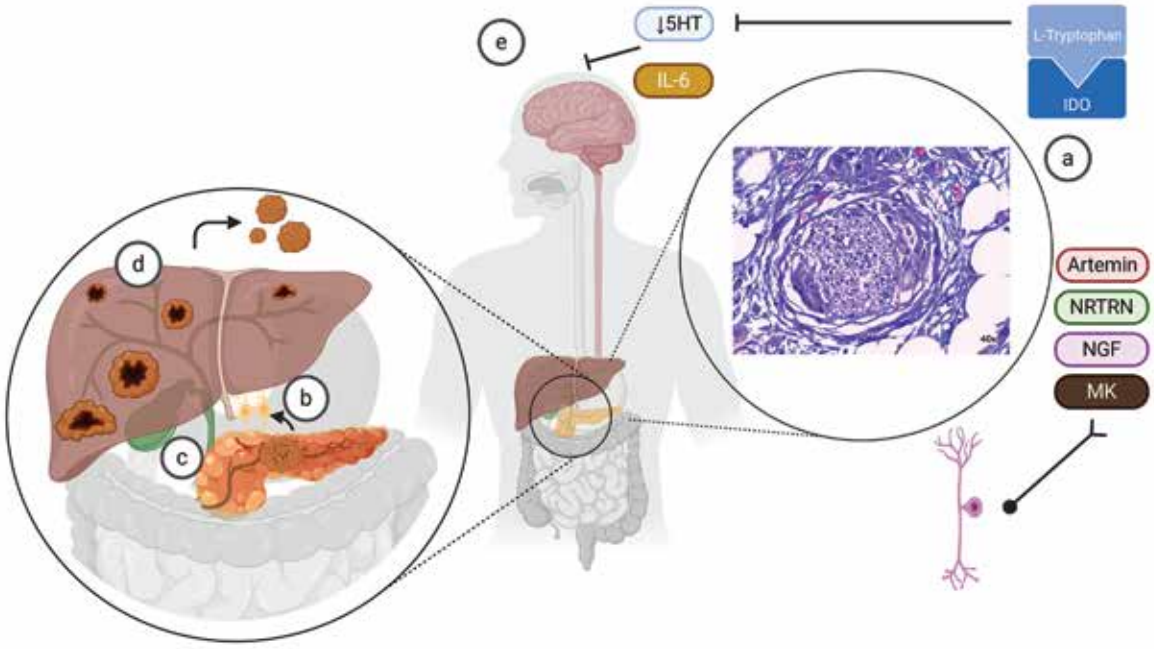

Fig. 1. *Main PCRP pathophysiological mechanisms. a) Pancreatic neuropathy. Interaction of pancreatic ductal carcinoma with nerves increases neural density and leads to nerve damage. These changes are promoted by growth factors, such as nerve growth factor (NGF), Neurturin (NRTRN), neurotrophic factor midkine MK and Artemin. b) Autonomic plexus invasion. Cancer may progress through retroperitoneal invasion of the celiac, splenic, and superior mesenteric plexus. c) Local progression. Pain may be related to malignant obstruction of pancreato-biliary tree with elevated intraductal pressure and intrapancreatic enzyme activation, as well as by small bowel edema and obstruction. d) Liver metastases and distant metastases are common during disease progression and may cause distention of liver capsule and pain. e) Pancreatic cancer related depression may be facilitated by high IL6 levels and overexpression of Indoleamine 2,3-dioxygenase (IDO), with subsequent disturbances in tryptophan and serotonin metabolism. In this complex pain model, it is likely that a combination of factors contributes to the individual painful experience.*
Source: biorender.com

peritoneal invasion of the celiac, splenic, and superior mesenteric plexus (23,34,35).

Loco-Regional Progression and Distant Metastases

Considering epigastric retroperitoneal location of the pancreas, other pain generators may develop during locoregional and distant tumor spread in patients with advanced PC, as part of the disease natural evolution. Autopsies series have established that the most common sites of metastatic disease are peritoneum, liver, and lung (36,37). Local pain may also be related to malignant obstruction of pancreato-biliary tree, biliary distention, and intraluminal activation of pancreatic enzymes. Biliary stenting with endoscopic retrograde cholangiopancreatography (ERCP) allowed a reduction in pain scores in patients with dilated biliary tree, up to 3 months in a prospective trial (38,39). Anterior extensive local progression may cause small bowel distension and severe, visceral pain. Multiple surgical or endoscopic decompressive measures have shown a potential therapeutic role in such cases (40,41).

PC Neurobiology

In addition to previously described anatomical factors, particular PC neurobiology plays a major role in PRCP as perineural tumor invasion of intrapancreatic nerves, neurogenic inflammation, and tumor metastases along extrapancreatic nerves are key features of pancreatic adenocarcinoma (42). Histologic infiltration of pancreatic cancer cells in nerves has been recognized as a distinctive characteristic of PC for almost 6 decades (43). Pancreatic adenocarcinoma present some of the highest incidences of perineural invasion (90%) (44-47). This phenomenon has been extensively studied elsewhere and has been called pancreatic neuropathy (34,47-51).

Pancreatic ductal adenocarcinoma cells are able to induce neuronal plasticity (52). Interaction of PC with nerves is known to lead to nerve damage; described morphological changes are disrupted perineurium, distorted integrity of the whole nerve, and severely axonal edematous appearance, as a result of the invasion by pancreatic cancer cells (53). Other well described features are increased neural density and hypertrophy, both of which correlate with the development of pancreatic neuropathic pain (48) (Fig. 2).

These abnormal changes are promoted by specific neurotrophic factors. Nerve growth factor (NGF) and its high-affinity receptor TrkA are both involved in stimulating epithelial cancer cell growth and perineural invasion. High levels of NGF/TrkA positively correlate with pain and negatively correlate to prognosis in pancreatic cancer (53,54). Other neurotrophic factors such as Neurturin (NRTRN) and its receptor glial-cell-line-derived neurotrophic factor receptor alpha-2 (GFRα-2), have been associated with a severe abdominal pain phenotype (55). Similar effects have also been found from neurotrophic factor MK (also known as a neurite growth promoting factor) and the Syndecan-3 receptor (56,57). Artemin and its receptors (GFRα3/RET) have been shown to be overexpressed in PC. In PC biopsies, Artemin mRNA expressions were significantly correlated with both neural hypertrophy and density, and correlated with the degree of pancreatic neural hypertrophy but not with PCRP (58-60). Variable expression of these neurotrophic factors and receptors contribute to the aggressive nerve lesioning phenotype of PC and the development of pancreatic neuropathy.

PC Associated Depression

Patients with PC have a high prevalence of depression. A meta-analysis of 6 prospective trials including 457 patients with PC estimates that 43% of patients experience depression after diagnosis (61). Current evidence suggests that pain and depression are highly intertwined and may co-exacerbate physical and psychological symptoms. Patients with pain and depression experience reduced physical, mental, and social functioning, as opposed to patients with only depression or only pain. Both conditions have individual and additive adverse associations with quality of life (18). Depression has also been shown to negatively impact survival outcomes in PC. A cohort study, which included 23,745 patients with a diagnosis of adenocarcinoma of the pancreas, established patients without depression had a median survival of 3.1 months, compared to 2.1 months for patients with depression ($P < 0.0001$) (62). A prospective cohort study of 108 PC patients suggested early psychiatric intervention in patients with PC may maintain health related quality of life (63). There has been increased support for the role of neuroinflammatory mechanisms as relevant factors in this dyad. Such changes may have an impact on the functioning of key brain regions ability to modulate emotional and nociceptive processing, thus, resulting in the behavioral, psychological, and physical symptoms observed in patients exhibiting depression and co-morbid pain (64). Several molecular mechanisms have been associated with PC-related depression, such as high cytokine levels

--in particular IL6-- and overexpression of Indoleamine 2,3-dioxygenase (IDO), an enzyme involved in tryptophan metabolism through the kynurenine pathway, with subsequent disturbances in tryptophan and serotonin metabolism. These biological based mechanisms are currently under research (10,61,65,66).

PCRP Treatment

Treating PCRP is a complex discipline that requires multidisciplinary assessment and treatment (67). Systemic opioids for severe pain constitute a standard of care and morphine has proven to be equally effective to oxycodone in this population (68). Protocol driven opioid management in this population achieves effective pain relief at 2 months in 42% of cases (69). Other medications such as tricyclic antidepressants or anticonvulsants have proven efficacy in neuropathic cancer related pain, but have yet to be extensively evaluated in PCRP, despite the acknowledged neuropathic pain component in this condition as previously discussed. A prospective randomized trial proved gabapentin to be effective in improving analgesia in patients with neuropathic cancer pain already treated with opioids, but most likely no specific PCRP were included in this study (70). Only a small case series of gabapentin use in PCRP have been published (71).

Disease modifying palliative interventions, such as gemcitabine or FOLFIRINOX chemotherapy, have poor effect on pain control and no improvement in health-related quality of life (72,73). Endoscopic treatment of ductal or biliary obstruction could aid in selected cases (38,39). Other techniques, such as conventional external radiotherapy, may possibly provide analgesia; nevertheless, adverse effects and appropriate access might limit its efficacy. Newer techniques such as intensity modulated radiotherapy, stereotactic radiotherapy, or celiac plexus radiosurgery may also have a role in selected cases (74-77).

Several invasive techniques have been traditionally advocated for PC pain treatment, in particular celiac plexus neurolysis and splanchnic nerves neurolysis (35,78,79). Different approaches and image guidance methods have been advocated as favorable, but statistical evidence is conflicting for the superiority of pain relief over systemic analgesic therapy, even though a reduction in systemic opioid has been proven (69,80-82). Studies suggest these procedures offer mixed results depending on tumor anatomic location. Neurolytic solution dispersion is unpredictable and likely not effective in cases with severely distorted anatomy, due to locoregional tumor progression (83). Although earlier procedures have been advocated and included in practice guidelines for endoscopic ultrasound, early intraoperative neurolysis in operable patients has not proven better pain control results and midterm outcomes of this neuro-destructive procedure are not consistently positive (84,85). More recently, neuromodulation techniques, such as spinal cord stimulation, have been considered in PCRP, although supplemental research is still needed, as this indication is still exploratory (86).

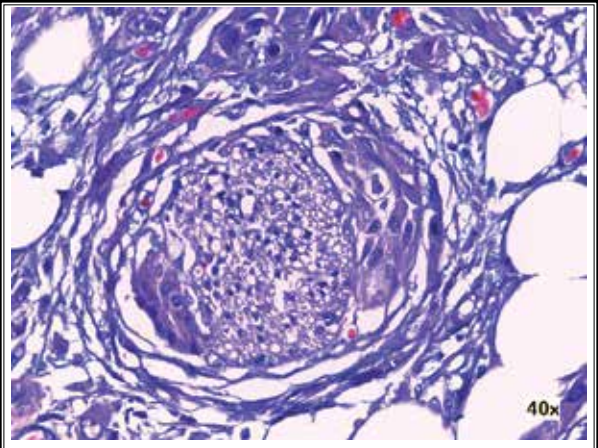

Fig. 2. *PC perineural invasion. Microscopic photography shows perineural invasion by pancreatic ductal adenocarcinoma. Hematoxylin & Eosin Stain.* Courtesy of Dr. Eduardo Alfaro.

Intrathecal Drug Delivery for PCRP

IDDS are an invasive pain treatment technique that implies implantation of an infusion system with a catheter placed accurately in the posterior subarachnoid space. This allows treatment of pain with precise dosage of analgesics to spinal dorsal horn fibers, bypassing the cerebrospinal blood brain barrier with minimal systemic levels of opioids (87-90). The first intrathecal use of bolus morphine for cancer pain analgesia was described by Wang in 1979 and in 1980 intrathecal analgesia for pancreatic cancer pain was described by Tung (91,92). Neuraxial infusion systems have now been available for more than 40 years (93). Since these seminal studies were published, they have confirmed that this is an appreciated option for the small proportion of highly distressed cancer patients who have exhausted all other analgesic treatments. Positive impact has been described in reduction of pain and quality of life outcomes (94,95). Main cancer related pain treat-

ment guidelines now have IDDS as an alternative for complex cases (96-98). Multidrug regimens including morphine, ropivacaine, and ziconotide allow for reduction of individual intrathecal drug doses (90,99). According to a study, standard placement for precise drug delivery to the posterior spine, close to T6, allowed for better pain control in 90% of patients with IDDS (100). Different retrospective, prospective, observational, and randomized controlled studies have shown its efficacy in treating cancer related pain syndromes. Eighteen studies of IDDS, including at least 236 PC patients, are hereby presented (Table 1). Despite the high burden of pain in PC, there are very few IDDS studies that have included significant numbers of such patients. The reason is unclear, as it is highly prevalent and frequently associated with severe pain, as previously noted (15-17).

A pivotal retrospective study by Gilmer-Hill evaluated the analgesic efficacy of intrathecal morphine by IDDS in 9 patients with PC, implanted over a 2-year period. Mean pre-implantation subjective pain scores were 8.7 and mean oral morphine equivalents 244 mg. According to the researchers, all patients experienced good to excellent relief of pain (2.3 pain scores after IDDS) (101). In a recent retrospective study, 93 patients with refractory PCRP (total therapy duration 10,300 IDDS days) were observed. Efficacy of IDDS were

Table 1. *Most relevant studies on IDDS in cancer pain and PC*

Authors	Year	Total implanted patients n = 1704	Patients with PC treated with IDDS n = 236 (%)	Global pain outcomes	Technical comments
Onofrio, et al (106)	1990	53	8 (15%)	67% were defined as having good or excellent results in the perceived quality of life. Mean treatment duration was 4 months.	IT Morphine sulphate
Gilmer-Hill, et al (101)	1999	9	9 (100%)	NRS decreased from 8.67 to 2.28, mean treatment duration 137.3 days. Median infusion duration 8 weeks in PC (1-13).	IT Morphine sulphate Systemic opioids stopped in 75% of patients. 15 cm of catheter inserted in the subarachnoid space from L5 S1.
Smith, et al (105)	2002	101	7 (6.9%)	VAS decreased from 7.57 ± 1.79 to 3.90 ± 3.42 at 4 weeks, compared to CMM (P = 0.055). Median daily systemic opioids had fallen from 250 mg to 50 mg for IDDS patients.	RCT during the first 4 weeks, all IDDS patients had IT morphine or hydromorphone. 15 of 51 (29%) had bupivacaine added, 1 droperidol, 1 clonidine.
Rauck, et al (123)	2003	119	N/A	NRS decreased from 6.1 ± 1.9 to 4.2 at 1 month (P < 0.01) and remained decreased through month 13 (P < 0.05). Overall success reported in 83%, 90%, 85%, and 91% of patients at months 1, 2, 3, and 4, respectively.	IT Morphine sulphate
Smith, et al (124)	2005	30	2 (6.7%)	VAS reduced from 6.2 ± 2.8 to 4.5 ± 2.7 for those whom CMM failed and crossed over to IDDS by 6 months (P = 0.011) ECOG 2-4 40%.	
Mercadante, et al (125)	2007	55	N/A	VAS reduced from 7.98 to 3.87 at 1 month and 3.92 at 3 months (P < 0.0001).	IT levobupivacaine 12.5-25mg/d and oral-intrathecal ratio of 100:1 morphine through intrathecal port.
Dupoiron, et al (119)	2011	97	20 (21%)	NRS reduced from 7.9 ± 0.27 to 3.65 ± 0.46 at 1 month, differences at 1, 2, and 3 months (P < 0.001).	Mean IT morphine 18.5 mg/d (0.3 - 100), Ropivacaine 13.2mg/d (0.4 - 56.2), Clonidine 10.8ug/d (2 - 44), Ziconotide 3.94 ug/d (0.25 - 19). Systemic opioids stopped in all patients.
Brogan and Winter (126)	2011	31	6 (19%)	NRS decreased from 6.5 to 3.1 at 4 - 6 weeks (P = 0.011). There was a reduction in total non-intrathecal opioid use, average of 796 mg pre-IT vs 64 mg post-IT (P = < 0.001). 50% of patients discontinued all non-intrathecal opioids.	
Huang, et al (99)	2015	36	1 (2.7%)	NRS decreased from 8.17 ± 0.51 to 2.50 ± 1.04 in morphine treatment group and from 7.78 ± 0.73 to 1.33 ± 0.77 in morphine + ropivacaine group (P = 0.001).	IT morphine dosage calculated using oral-intrathecal ratio of 300:1, combined in 51% of patients with ropivacaine (initial dose 4.5 mg/d). IT administered through a port.

Table 1. *Most relevant studies on IDDS in cancer pain and PC (continued)*

Authors	Year	Total implanted patients n = 1704	Patients with PC treated with IDDS n = 236 (%)	Global pain outcomes	Technical comments
Brogan, et al (120)	2015	58	5 (8.6%)	Worst pain NRS decreased from 8.32 ± 1.73 to 4.98 ± 2.92 ($P < 0.001$)	A patient-controlled intrathecal analgesia was used for the treatment of breakthrough pain. 50% of patients had discontinued all non-intrathecal opioids, 91% had either IT morphine or hydromorphone. Median IT morphine was 3.63 mg/d. 42% received a mixture of opioid and bupivacaine (0 - 30 mg/d). Other medication included ziconotide, fentanyl, clonidine, baclofen.
Mitchell, et al (127)	2015	22	1 (4.5%)	Worst pain NRS decreased from 9.2 to 4.27 at 1 month ($P \leqslant 0.05$) and 6.7 to month 6 ($P \leqslant 0.05$).	IT morphine using the ratio of 1:300 of oral morphine. Levobupivacaine initial dose of 12mg/24h. The patient typically receives no regular oral opioid medication. Breakthrough opioid available.
Liu H, et al (95)	2015	84	N/A	Average NRS decreased from 7.2 ± 1.2 to 2.6 ± 0.4 ($P < 0.05$). Decreased pain intensity was maintained at approximately the same magnitude through month 9.	IT morphine administered through a port.
Zheng, et al (114)	2017	53	8 (15%)	NRS reduced from 8.5 to 3 (IQR: 2 - 3) at 1 month ($P < 0.05$) and 3 (IQR: 3 - 4) at 3 months ($P < 0.05$).	The tip of the catheter was placed between T7 -T10. Patients were suggested to stop taking opioids by other routes. IT morphine using a 1:300 of oral morphine administered through a port.
Sayed, et al (128)	2018	160	32 (20%)	NRS reduced from 7.1 to 5.0 at 1month. Median decrease in NRS was 2.5 after 1 month ($P < 0.01$). Pain scores 3 months post-implantation did not significantly differ from 1 month post-implantation.	66% percent of patients received IT bupivacaine, in addition to IT opioids. 87% received a patient-controlled bolus device.
Carvajal, Dupoiron, et al (100)	2018	93	93 (100%)	Severe pain decreased from 89.2% before surgery to 4.5% after 1 week, 6.7% after 1 month, and 10.3% after 3 months of IDDS implantation ($P < 0.01$).	All systemic opioids were stopped. Catheter most commonly placed at T6. A multidrug regimen, including morphine, ropivacaine and ziconotide, was prescribed systematically. 75% received a patient-controlled bolus device. 25% of patients treated through port.
Brogan, et al (129)	2019	51	6 (11.8%)	Average pain decreased from 5.86 (1.8) to 4.54 (2.72) at 8 weeks.	2 patients followed to 8 weeks, catheter placed at T6 and T9. Treated with combined morphine-bupivacaine or hydromorphone.
Puntillo, et al (104)	2020	60	9 (15%)	Mean VAS reduced from 88 ± 20 mm to 44 ± 9 at 56 days ($P < 0.001$).	Systemic opioid stopped. Short-acting oral morphine dose used for breakthrough pain. The tip of the catheter was placed near dermatomal level of the worst pain. A multidrug regimen was prescribed. IT morphine was calculated using a 400:1 oral: IT ratio for IT. Ziconotide was started at 1.2 µg/day. Levobupivacaine was started at 3 mg/day. IT treatment through port.
Stearns LM, et al (107)	2020	592	49 (8.3%)	Cohort of 283 patients for whom baseline pain scores were available. Average pain decreased from baseline (6.6 ± 2.4) to 6 months (5.5 ± 2.6, $P = 0.0007$) and to 12 months (5.4 ± 2.5, $P = 0.0026$). Patient-reported quality of life, as indicated by the EQ-5D Index value and the EQ-5D Health-VAS, demonstrated statistically significant improvement compared to baseline at 6 months (n = 41).	RCT

*CMM comprehensive medical management, †IQR interquartile range, ‡ N/A Data not Available, NRS Numeric Rating Scale, VAS Visual Analog Scale, RCT Randomized controlled trial

evaluated over an 11-year period, using a combination drug regimen with catheters placed mainly at T6. In this study, all patients suffered from severe pain or inacceptable adverse effects from systemic treatment before implantation (median Numerical Rating Scale 8 out of 10), despite a median 360 mg oral morphine equivalent daily dose. IDDS was associated with clinically and statistically proven pain relief after 1 week, 1 month, and 3 months (median change in NRS -6; $P < 0.001$). Severe pain decreased from 89.2% before surgery, to 10.3% after 3 months of IDDS implant ($P < 0.01$). It is noteworthy that frailty and advanced disease were common in these patients, as 88.2% of patients had metastatic disease at IDDS surgery, 76.3% had low performance status, and 58.1 % were cachectic (100).

Most studies of IDDS in PCRP evaluate outcomes on pain by unidimensional scales, such as the Visual Analog Scale (VAS). Other relevant variables, like cancer stage and location, and comorbidities, such as depression, are not reported in most studies. In the same way studies are heterogeneous regarding IT prescription, heterogeneous IT drug delivery regimens, catheter placement, and pump flow may account for results variability, as these tend to have later impact on drug distribution (102,103). Other non-controlled variables that may impact overall results are systemic analgesics, which in some studies are stopped at implantation (100,104), but in others are maintained (105,106). Few studies report relevant outcomes, such as quality of life (105,107), and psychological aspects relevant to pain outcomes are underreported.

Although IDDS, as previously stated, is considered a relevant alternative for pain management in PCRP, expert consensus advocates for a much wider application of IT therapy to provide meaningful analgesia for patients with cancer pain, including those at the end of life (108). Expected survival time is to be considered when deciding the best adapted technique. Existing randomized controlled trials have previously excluded patients for IDDS pump implantation with life expectancies shorter than 3 months (105). This particular duration is not based on anticipated clinical efficacy, but was adopted from earlier studies comparing cost effectiveness of tunneled intrathecal catheters and fully implantable pumps. Implantable devices may be more suited for patients with poor functional status and high risk of surgical complications. Considering this, IDDS needs to be discussed earlier as disease progression may limit access to this therapy if offered too late. Presently, it is generally accepted that electronic infusion pump IDDS should only be implanted if patients are anticipated to live more than 3 months. Case discussions and multidisciplinary team decisions are key, as intrathecal therapies should be used at an appropriate time in the algorithm and not as a salvage treatment (109). PC patients will often be considered category 1 (patients with imminent death or relatively short life expectancy, with palliation as primary objective) (109).

In cases of end-of-life pain, other less complex and invasive methods, such as intrathecal external catheter or subcutaneous port, may be considered more appropriate despite a higher infection risk (110-112). In studies that considered this technique, 24.7 - 100% of patients were treated using a catheter adapted to a subcutaneous port and an external pump (95,99,100,104,113,114). These systems, although technically simpler, may imply a burden of care that precludes its use for patients with better functional status. Other considerations, in addition to cost effectiveness, include: patients desires, surgical risk, recovery time, and functional status(109).

Discussion with oncology team and palliative medicine may help in preventing surgical complications, as studies show 23 - 57% of patients receive chemotherapy during the month previous to surgery, and up to 65% may receive chemotherapy during the first month after surgery (100,115). When considering patients, prognostic scales ,such as palliative prognostic index, PRONOPALL, or pancreatic cancer predictive score of survival (PCPSS), may help guide clinicians to define the best treatment modality. PCPSS score is calculated by attributing a value of 1 for pain, ascites, and weight loss, and 2 for the presence of metastases. Patients with a score > 2 had a median survival of 2 ± 0.5 months and patients with a score ≤ 2 had a median survival of 6 ± 0.6 months ($P < 0.0001$) (116-118).

Finally in light of the aggressive nature of the disease and poor overall survival clinicians may want to consider a close medication regimen adaptation or the development of combination therapy strategies, as frequently reported (99,100,104,113,119,120). Optimal IT drug regimen for PCRP is not as yet known. Combination strategies using an opioid, a local anesthetic, and N-type voltage-gated calcium channel blocker have been shown to be stable and have been used with success (100,119,121,122).

Limitations

IDDS heterogeneity regarding disease stage, patient population, and technical aspects, such as cath-

eter placement and treatment regimen, do not allow for integration of studies.

Conclusions

PCRP treatment is a highly complex endeavor considering patients are affected by severe pain, poor prognosis, and a lack of disease modifying strategies. This debilitating condition negatively impacts patients' quality of life and survival outcomes, and contributes to a decline in patients' functional status that can adversely influence access to disease-modifying treatment. We have reviewed anatomical and biological factors that determine PCRP evolution and discussed the role of IDDS in achieving optimal pain relief.

IDDS is a valuable treatment for patients with PCRP. Studies including patients with PC are mainly retrospective, with a low inclusion rate, but consistently show a positive effect on pain outcomes. Most studies of IDDS in PCRP evaluate outcomes on pain using one-dimensional pain scales such as VAS. Other relevant results, such as performance status or quality of life, are not frequently reported. Burden of disease variables, such as cancer stage, location, and comorbidities, such as depression and systemic analgesia co-prescription, are usually not reported in these studies. Similarly, most studies do not precisely report IDDS relevant variables, such as catheter position and pump flows, and devices vary across studies.

This review analyzes both past and current literature with a critical analysis of findings and respective recommendations. In addition, based on review of the literature, we provide therapeutic keys for the consideration of pain physicians when dealing with this patient population.

Future studies regarding impact of IDDS on pain control and quality of life in this particular population may help clinicians in deciding the optimal time and approach for IDDS. The studies should report data on particular disease, comorbidities, and treatment regimens.

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