Review

Chronic pain syndrome in patients with pancreatic cancer: individual therapy and its pathogenetic background

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Abstract: This review presents the results of recent studies on the role of pathogenic mechanisms of chronic pain syndrome in patients with pancreatic cancer. The authors searched Russian and international databases, including MedLine, PubMed, NEL elibrary.ru, Wiley Online Library, Web of Science, Oxford University Press, SAGE Premier, for the period from 1996 to 2016 (10 years). Our results demonstrate the preconditions for multimodal analgesic therapy in anesthesia and pain treatment. We show the key role of selecting basic pharmacological groups of drugs for the patients with pancreatic cancer with chronic pain syndrome. The dependence of patient survival on the intensity, diversity and complexity of pancreatic pain in pancreatic cancer means that individual therapy is extremely important as inadequate pain relief can have profound negative effects on the psychosocial and physical well-being of pancreatic cancer patients and their relatives.

Keywords: pancreas cancer, chronic pain syndrome, review, opioid analgesics, individualization of analgesia.

Pancreatic cancer is a leading cause of deaths among the cancers of gastrointestinal tract organs. It ranks fourth in men and fifth in women among all death causes after lung, stomach, colorectal and prostate cancer, with the incidence equal to 4.2% in the world, including that in Russia [1]. Pancreatic cancer is a malignant neoplasm with high mortality, early metastases and the lack of proper efficiency when chemotherapy, radiation therapy and combination therapy are applied [2]. The median survival of patients with inoperable pancreatic cancer is 5.8 months [3], while the median survival for resectable forms can be from 12 to 15.9 months [4].

Patients with inoperable pancreatic cancer experience high rates of late diagnosis, inoperable forms and recurrence after surgical treatment (80% cases). The increasing incidence of pancreatic cancer in Russia and across the world makes essential palliative medical care, including pain therapy [5]. Treating pain related to pancreatic cancer is possible through pharmacological and endoscopic treatment.

This paper seeks toreview Russian and international research on the occurrence mechanisms and feasibility of chronic pain relief for the patients with pancreatic cancer.

The authors searched Russian and international databases, including MedLine, PubMed, NEL elibrary.ru, Wiley Online Library, Web of Science, Oxford University Press, SAGE Premier for the period from 1996 to 2016 (10 years). The search for publications was carried out using keywords such as pancreas cancer, chronic pain syndrome, review, opioid analgesics, individualization of analgesia in Russian and English.

The anatomical localization of the primary pancreatic tumor has a significant effect on corresponding pain patterns [6]. Anatomically close location of the pancreas to the organs of the hepato-biliary duodenal zone and direct contact with the vascular bundle, and nerve trunks determines the tumor process and chronic pain syndrome regardless of the size of the tumor [7]. Pain syndrome in patients with advanced pancreas cancer is extremely severe. As a rule, it is accompanied by a pharmacy-resistant clinical manifestation which is often associated not only with tolerance, but also with the appearance of numerous adverse effects of opioid therapy [8]. Pain syndrome in advanced pancreatic cancer is registered in 80% of patients along with abdominal distension, belching, heartburn, abnormal stool, cancer-related weakness and weight loss [9], and it is associated with decreased survival [10]. Only 30–40% of patients with pancreatic cancer have moderate or severe pain. From eighty to ninety percent of patients with common forms experience extremely severe pain until death [11, 18]. Several studies have shown that the activation of nociceptive pathways, involvement of inflammatory mediators, and

sensitization of central and peripheral nervous systems play a huge role in the pain formation in pancreatic cancer [12]. The origin of pain in pancreatic cancer can be somatic, visceral, neuropathic and mixed. Peripheral nociceptive neurons are located at the level of T12–L2. They are in contact with the second-order neurons through the Th5-Th12, and are also in contact with the neurons of the third order, located in the brain. The interaction of the groups of neurons results in the development of central sensitization [13]. Somatic and neuropathic pain can occur due to the spread of a tumor into surrounding peritoneum, retroperitoneal tissue, bones and, in the latter case, nerves such as the lumbosacral plexus. Neural invasion and severe pain are common features in patients with pancreatic cancer [14].

Central sensitization predetermines the mandatory prescription of anti-nociceptive drugs (gabapentinoids, antidepressants, anticonvulsants, etc.) for chronic pain syndrome [15].

Other types of painsuch as post-chemotherapy syndromes that cause mucositis and enteritis, may also occur due to therapeutic interventions [16]. Progress in understanding the mechanisms of pain, along with the assessment of new therapies, both pharmacological and endoscopic, can contribute to improving the quality of life and patient survival [10]. Chronic pain in patients with pancreatic cancer significantly impairs the quality of life [17, 18]. Neural invasion of cells in the intrapancreatic pancreas is observed in 100% of patients with pancreatic cancer [19, 20]. Cancer cells spread through the intra- and per pancreatic nerve trunks into the retroperitoneal space, limiting the effectiveness of resections in case of local recurrence with a negative impact on overall survival [21]. The effect of the presence of distant metastases on the intensity of chronic pain in patients with pancreatic cancer is controversial [23]. The intensity of pain in pancreatic cancer is diverse, and mainly depends on the type of tumor and its anatomical localization [24]. Thus, patients with tumors in the head of the pancreas have lower pain intensity than patients with cancer in the body or tail of the pancreas, regardless of the stage and size of the tumor. Currently, a variety of existing pro-inflammatory ligands and their receptors play a role in the initiation of pain in pancreatic cancer [24]. It is known that the level of interleukin-6 (IL-6) and interleukin-10 (IL-10) is significantly higher and the level of transforming growth factor beta (TGF-beta) is significantly lower in patients with pancreatic cancer than that in healthy volunteers. The severity of depressive symptoms significantly correlated with the level of IL-6, while hopelessness was associated with the level of interferon alpha (IFN-alpha). Pain, fatigue, and sleep disorders were associated with a number of cytokines, including interleukin 1-beta (Il-1beta; pain intensity), interleukin 4 (IL-4; pain intensity and overall sleep quality), interleukin 12p70 (IL-12p70; pain intensity), and TGF-beta (fatigue intensity) while anxiety was not associated with any of the cytokines [25]. The structure of pain in pancreatic cancer is mainly related to neuropathic pain due to known neuroplasticity changes [24, 26] with the development of pancreatic neuritis and perineural invasion by cancer cells [26]. Nerves in the pancreatic tumor tissue are a rich source of neurotrophic factors such as nerve growth factor (NGF), neurotrophic glial cell factor (GDNF), neural chemokines such as fractalkine (CX3CL1), autonomous neurotransmitters such as noradrenaline. These factors can enhance invasiveness of cells via matrix metalloproteinases (MMP). A pronounced correlation of neurogenic invasion by pancreatic cancer cells suggests the potential presence of a

triangular connection between nerves, cancer cells and stromal cells, such as myofibroblasts and stellate pancreatic cells [22], contributing not only to the spread of the neoplastic process, but also to neuropathic pain syndrome. Moreover, an increased expression of fractalkine transmembrane chemokine receptor CX3CR1 (CX3CR1 receptors) in pancreatic tissues is associated with a more pronounced neurogenic invasion and earlier local recurrences of tumors [27], reducing survival. Thus, chemokines play a key role in the interaction of nerves and cancer cells. In addition, pancreatic neuropathy is characterized by numerous molecular and morphological changes in peripheral and central nervous systems [28].

An increase in peripheral nociceptive signals is mediated by neurotransmitters and neurotrophic factors, along with the damage to nerves and neuroplasticity changes in the neurons of dorsal horns of the spinal cord [28].

Such neuropathic changes were not registered in other pancreatic tumors, such as cystadenoma, intraductal papillary mucinous neoplasia, neuroendocrine neoplasia, and ampullar cancer [29]. Tumors in the body and tail of the pancreas are associated with more severe pain, which is especially important given the most frequent prevalence of this localization (63%) among all pancreatic tumors. The frequency of painless pancreatic cancer was 39% for tumors localized in the body of the pancreas, 42% for tumors in the tail, and 51% for tumors in the head of the pancreas [26]. The most intense pain was recorded for tumors in the body (16% vs. 14.8% in the tail with no statistically significant difference) [23]. 35.9% of patients with a tumor in the pancreatic head experienced mild pain, compared with 44.2% of patients with a tumor in the pancreas body and 43.2% of patients with a tumor in the tail of the pancreas. The incidence of patients with moderate and severe pain was significantly higher in pancreatic body cancer compared with pancreatic head cancer or tail cancer (23.4% vs. 14.0% and 17.5%, respectively). There is no significant difference in chronic pain syndrome between the invasive and non-invasive forms of the intraductal papillary-mucinous tumor. 64% of patients with low staging and 59% with high staging of neuroendocrine neoplasia of the pancreas do not manifest chronic pain syndrome, which is also the case for most patients with ampillary pancreatic cancer (61.4%).

Patients with more malignant tumors showed significantly higher levels of moderate and severe pain compared with patients with benign lesions of the pancreas (14.4% vs. 6.7%, p<0.05) [23]. Moreover, patients with tumors of the body and tail of the pancreas are characterized by a higher staging [31] and greater consumption of analgesics. Patients with a longer history of the disease are prone to more severe pain (moderate/severe pain in 5.9% of tumors at stage 2, 16.0% at stage 3 and 36.4% at stage 4). However, over 60% of patients with stage 2 pancreatic cancer had chronic pain syndrome, while 47.9% of patients with stage 3 and 36.4% of patients with stage 4 had no chronic pain syndrome [23]. Regional and/or distant metastases did not impact the presence or severity of pancreatic pain in patients with pancreatic cancer [23]. Moreover, the occurrence and intensity of chronic pain syndrome does not depend on the histological structure of the tumor. Data on the effect of diabetes mellitus on the presence or severity of pancreatic pain in patients with pancreatic cancer are contradictory due to a lack of communication, [23] or a lower incidence of abdominal pain [31] with a higher prevalence of perineural invasion. The pain intensity was found to be associated with survival disorders in pancreatic cancer. Patients without pain

had a 3-year survival rate of 27.9%, with mild pain — 15.3%, with moderate and severe pain 15.2%, respectively [23]. There was no statistically significant difference (p>0.05) in survival between patients with tumor localization in the body and tail and patients with tumor localization in the pancreatic head [6]. Thus, pancreatic pain in pancreatic cancer is diverse and multicomponent. The umbrella term 'cancer pancreatic pain' is difficult to apply to various types of pain syndrome. Abdominal pancreatic cancer pain is a predictor of poor outcome, as shown in many studies [30]. Since the pancreas is an integral part of the digestive system, the presence of gastrointestinal symptoms will be an integral part of the clinical picture of pancreatic cancer. Jaundice is a clinical symptom in 51–72% of patients with inoperable pancreatic cancer and develops in more than 80% of patients [32, 33]. Its occurrence is more frequent in patients with pancreatic cancer [6]. Obstructive jaundice leads to poor fat absorption and itching due to decrease in the excretion of bile acids into the duodenum, causing anorexia and diarrhea, as well as cachexia. Fat malabsorption also reduces the ability to absorb fat-soluble vitamins, including vitamin K, which leads to coagulopathy and an increased risk of bleeding [34]. Uncorrected cholestasis can lead to hepatic dysfunction and even liver failure, which can disrupt the dosage of analgesics and lead to undesirable effects. Patients with biliary obstruction are at an increased risk of cholangitis with anamnestic instrumental intervention to treat biliary tract [33]. Sixty-five percent of patients with pancreatic cancer will experience symptoms of fat malabsorption, and 50% will also have protein malabsorption [35]. This should be considered when determining the dose of nonsteroidal anti-inflammatory drugs and opioid analgesics. Forty percent of patients with pancreatic cancer experience nausea and vomiting. Constipation is a frequent complication of opioid therapy, and its prevention should begin at the start of opioid therapy. Other causes of constipation in patients with pancreatic cancer may include such effects as a diet low in fiber, decreased fluid intake, decreased physical activity, and the effects of bed rest. More serious causes may include various metabolic disorders and even intestinal obstruction. Indigestion, diarrhea and changes in the normal functioning of the intestines are not uncommon in pancreatic cancer. Weight loss and cachexia occur in 90% of patients with pancreatic cancer. The true cause of emerging ascites in pancreatic cancer is not completely understood, and is typically associated with the presence of lymphatic or peritoneal metastases. Fatigue syndrome, often described as a loss of normal energy levels, influences mental processes. It is most often debilitating in these patients [35].

Thus, a rapid invasion of the pancreatic tumor in nearby organs and nerve trunks is a cause of pain in 80–85% of patients. It is characterized by high intensity, pain recurrence, the obligatory presence of a neuropathic component, and the need for pain relief [18]. The World Health Organization (WHO) universal pain relief ladder does not allow for the proper control of the symptoms of pancreatogenic tumor-induced pain syndrome, which can be explained by various factors. These can be a combination of pain varieties in a patient, various thresholds of sensitivity and genetic factors [37, 38]. Individualized pharmacotherapy is the most effective method of treatment of pain in pancreatic cancer. To alleviate pain, multimodality is usually required, including such methods as modification of the pathological process, interruption of pain pathways and an increase in the pain threshold. Since less than 20% of patients have localized forms of pancreatic cancer

with operative treatment options, pain management remains the "better support", the only viable strategy in everyday clinical practice [18]. Currently, the methods of endoscopic treatment, along with pharmacotherapy, can reduce the overall consumption of opioids and related side effects [36]. Pain relief in patients with pancreatic cancer is achieved by such innovative methods as an intra-operative chemical splanchectomy, an external, percutaneous radiofrequency ablation of splanchnic nerves, percutaneous (or ultrasound or CT-oriented) neyrolysis, transgastric neurosis of the celiac plexus with endoscopic ultrasound, endgastric ultrasound; plexus [39,40]. Literature shows the preservation of analgesic efficacy of innovative methods of anesthesia as an additional alternative to pharmacotherapy in 92% of patients for three months after their application [38, 41]. Half of the patients with chronic pain syndrome related to pancreatic cancer require strong opioid analgesia, such as drugs of the third stage of the WHO analgesic ladder. Morphine sulfate, a classic strong opioid, is an important drug of choice for analgesic treatment of pancreatic cancer [16], and it is used more frequently than tramadol and codeine due to their lower analgesic potential and intense pain in pancreatic cancer. The transdermal therapeutic system with fentanyl and buprenorphine is an alternative to morphine for pain relief in pancreatic cancer in patients with preserved subcutaneous fatty tissue [42]. Several mechanisms of pain (obstruction of the pancreas, pancreatic neuropathy, and central sensitization) determine the mixed nature of pain. Methods of treatment should include drugs for stopping the neuropathic component of pain along with strong opioids [10, 43]. A low body mass index may determine a decrease in the rate of absorption of fentanyl from transdermal therapeutic systems, which is especially important in anorexia/cachexia syndrome and cancer-related weakness [44]. Hypoalbuminemia (albumin less than 3.5 g/dl) determines a lower plasma concentration of opioids [44]. In everyday clinical practice, adequate analgesia may require a higher dose of opioids related to low albumin levels, while a higher dose can determine the toxicity of opioid and non-opioid analgesics. Oxycodone-naloxone has a reduced number of side effects and it is also important for anesthesia in patients with pancreatic cancer [45]. It involves a lower risk of drug interactions with adjuvants due to the fact that it differs from other opioids in its transport function [45]. To reduce tolerance, we recommend using opioidrotation, taking the dose into account. Recommendations for opioid therapy inform that the conversion rate of oral morphine sulfate and transdermal fentanyl is 100: 1; that of oral morphine sulfate and transdermal buprenorphine is 75:1, that of oral morphine sulfate and oral hydromorphone is 5:1, that of oral morphine sulfate and oxycodon is 1.5:1 [46]. Tapentadol, a new strong opioid and a mu-opioid receptor agonist, should be also used to treat severe chronic pain as it is also a norepinephrine reuptake inhibitor [47]. Intranasal fentanyl is effective in the treatment of opioid-tolerant patients due to its rapid onset and short duration of action, non-invasiveness, high bioavailability, and the absence of first-pass through the liver [46]. A lack of the intranasal form of fentanyl in Russia makes it impossible to use it in breakthrough pain on a background of pancreatic cancer. The presence of exocrine pancreatic insufficiency observed in pancreatic cancer in 80–90% of patients, and in inoperable pancreatic cancer in 50–100% patients, respectively [48], decreases the effectiveness of narcotic and non-narcotic analgesics [49]. Total or partial resection of the pancreas is another risk factor for the development of functional

insufficiency [50]. Reducing the motor-evacuation function of the gastrointestinal tract, the development of excess bacterial growth syndrome, changing the pH in the lumen of the small intestine and reducing pancreatic secretion leads to changes in pharmacokinetic properties [51], which is another consideration in the treatment of breakthrough pain. It is important because parenteral forms have advantages over existing high-speed enteral forms for the treatment of breakthrough pain in patients with pancreatic cancer. The development of atrophic enteritis as a result of the syndrome of excessive bacterial growth, a decrease in bicarbonate production by the pancreas are the factors that reduce the effect of analgesics [52]. A decrease in pancreatic lipase excretion leads to the impaired absorption of lipophilic analgesics (transdermal forms) and gabapentinoids [49]. Thus, all patients with pancreatic cancer need constant enzyme replacement therapy, as well as control and correction of glycaemia during the development of secondary diabetes mellitus. It also means that the palliative treatment for pancreatic cancer should include proton pump inhibitors, antispasmodics, and somatostatin analogues. Comorbidity and a need for concomitant andpalliative therapy predetermine poly-pharmacotherapy with a possible risk of drug interactions. For example, the use of CYP3A4 (isoenzyme 3A4 cytochrome P450) (voriconazole, ketoconazole, grapefruit juice) with transdermal fentanyl strong inhibitors may lead to respiratory toxicity or other types of toxicity. The use of strong inducers (rifampicin, carbamazepine and phenobarbital) may be ineffective, decreasing the effect of opioids so it is necessary to take into account the interaction of drugs when planning analgesic therapy. Tamoxifen, diclofenac, naloxone, carbamazepine, tricyclic antidepressants and benzodiazepines are all inhibitors of the enzyme metabolism of morphine sulfate UGT2B7 (isoenzyme of the family uridine-5-diphosphate glucuronosyltransferase), which can lead to increased opioid sensitivity and undesirable reactions in patients with pancreatic cancer receiving morphine sulfate [52]. However, the glucuronidation of morphine sulfate minimizes the possibility of pharmacokinetic interactions compared with the CYP-mediated metabolism of fentanyl, oxycodone, buprenorphine and tapentadol. However, there remains a possibility of pharmacodynamics interactions of opioids with adjuvant drugs during palliative therapy [52].

Conclusion

The results of the review demonstrate that palliative therapy should be maintained taking into account a comprehensive assessment of various factors such as severity of chronic pain syndrome, its intensity, pathogenic mechanism of pain formation, tumor localization, anamnestic duration of the disease, the previous therapy, somatic pathology, organ function, and possible drug interactions.

Patients with pancreatic cancer experience severe pain of mixed nature. The pain is of pronounced intensity, with the obligatory presence of a neuropathic component. It is resistant to pharmacotherapy so that multicomponent treatment should be applied. The pain is more intense if the disease lasts longer (a direct relationship between the intensity of pain and disease duration can be observed) and the pain has pronouncedlocalization. The dependence of patient survival on the intensity, diversity and complexity of pancreatic pain in pancreatic cancer means that individual therapy is extremely important as inadequate pain relief can have profound negative effects on the psychosocial and physical well-being of pancreatic cancer patients and their relatives.

We recommend individual therapy due to a variety of contributing factors, such as the pathogenic mechanism of pain formation, somatic pathology, and individual sensitivity to opioid therapy.

Conflict of interest: none declared.

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