

EDITORIAL

Pain in Pancreatic Cancer: Does Drug Treatment Still Play a Role?

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Disabling pain together with cachexia is the most important symptom in patients with pancreatic cancer. Abdominal pain is a common debilitating symptom quickly leading to deterioration of the quality of life and performance status [1]. Although only 30-40% of patients report moderate to severe pain at the time of diagnosis, more than 80-90% of them with advanced disease experience severe pain before death [2]. Pain is generally transmitted through the celiac plexus which harbors sympathetic fibers carrying nociceptive information from the pancreas and surrounding organs. More infrequently, pain results from pancreatic duct obstruction and associated pancreatitis; this type of pain usually appears after meals, thus increasing the continuous pain related to the infiltration of the peripancreatic nervous plexus [3].

Management of pancreatic cancer-related pain is difficult, representing one of the main aspects of comprehensive management of the disease and should be started as soon as possible. In planning effective treatment, it is important to assess the nature of each type of pain (somatic, visceral, neuropathic or mixed). For example, patients with marked anxiety and/or depression may need at least 2-4 weeks of antidepressants to obtain optimum results, whichever analgesic treatment is chosen. Assessment of pain includes its quantification with a specific pain-score-scale and periodic reassessment is a continuing necessity as old pain may get worse and new types may develop. Since fewer than 20% of patients present with localized, potentially curable tumors, pain treatment still remains the mainstay of "best supportive care", very often the only viable strategy in daily clinical

practice [1]. Relief of pain usually requires a multimodality approach including: a) modification of the pathologic process, b) interruption of the pain pathways and c) elevation of the pain threshold. Analgesia can be achieved through the utilization of drugs (pain pharmacotherapy) or by means of procedures leading to neurolysis of the celiac plexus. In recent decades, great emphasis has been placed on celiac ganglion neurolytic block, as some studies have shown that, in inoperable pancreatic cancer, pain relief with analgesic drugs is often inadequate [4]. In synthesis, neurolysis can be achieved by means of four techniques: 1) intraoperative chemical splanchnicectomy, 2) percutaneous (computed tomography or ultrasound-guided) block, 3) endosonographically-guided block and 4) thoracoscopic splanchnicectomy [5]. Of course, all these procedures are invasive with full relief of pain obtained in only a small percentage of patients. On the contrary, a decrease in opioid dosages is achieved in almost 50% of patients and is effective for 3-4 months [6]. Controversy also exists as regards the timing of the neurolytic block, i.e. late (only after full failure of major analgesics) or early (before the onset of incapacitating pain) [4, 5]. Therefore, standardization of these alternatives to analgesic drug treatment is still lacking and the indication often remains more related to the presence of local expertise and feasibility than to objective requirements. These difficulties in attempting to interrupt the anatomical pain pathways give utmost importance to the need for elevation of the pain threshold. Concerning this, the utilization of analgesics is simply one way of elevating the patient's pain threshold, thus reducing the perception of pain.

Analgesic Drugs

As a rule for any kind of cancer pain, analgesic drugs usually give adequate relief provided that the "right" drug is administered in the "right" dose at the "right" time intervals [7]. Different modalities of administration do exist: a) by mouth (oral is the preferred route for analgesics, including morphine), b) by the clock (persistent pain relief requires preventive therapy; this means that analgesics should be given regularly and prophylactically; "on-demand"

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medication must be avoided) and c) by the ladder. The three-step WHO analgesic ladder based on pain intensity has been adopted worldwide. Non-narcotic drugs are indicated (non-steroidal anti-inflammatory drugs; NSAIDs) in step #1, mild opioids (e.g. codeine, tramadol) in step #2 and strong opioids (e.g. morphine) in step #3. If a drug fails to give relief, one must move up the ladder whereas to move laterally in the same efficacy group is not indicated.

Non-opioid (non-narcotic) analgesics are effective when administered as the sole drug for mild pain (WHO step #1) but they may be combined with opioids to treat moderate to severe pain (WHO step #2). NSAIDs demonstrate analgesic, anti-inflammatory and antipyretic activity by inhibiting prostaglandin synthesis from arachidonic acid via the cyclooxygenase pathway. NSAIDs do not help in the visceral pain of pancreatic cancer; however, they may be useful adjuncts in relieving abdominal wall pain or bone pain resulting from the vertebral spread of the disease.

Opioid analgesics are the mainstay in the management of moderate to severe pancreatic cancer pain because of their effectiveness, ease of titration and favorable risk-to-benefit ratio. They should be used early and liberally without undue concern about habit formation or physical dependence. Weak opioids are codeine and tramadol; strong (high-power) opioids are morphine, oxycodone, hydromorphone, methadone, buprenorphine and fentanyl. In patients with high-intensity pain (WHO step #3), high-potency opioids can be utilized safely, with an increasing dosage, until a satisfactory analgesic level is reached. Strong opioids do not have a ceiling effect to their analgesic efficacy, and will not reverse or antagonize the effects of other opioids within the class. These properties allow increasing the dosage without limits (theoretically). In clinical practice, the only real limit is related to the appearance of uncontrolled side effects. Morphine is the therapy of choice. Rapid action (fast release) preparations are useful for titration of the efficacious dose; slow release formulations are useful for chronic administration; 10 mg tablets of morphine every 4 hours may be prescribed as an initial dose. Valuable alternatives to morphine are oxycodone (fast release preparation associated with paracetamol) and hydromorphone (five times more active than morphine). Transdermal buprenorphine or fentanyl patches are useful for stable pain for patients unable to eat or those in a state of continuous vomiting or intestinal obstruction [8]. Association with antidepressant drugs or gabapentin, pregabalin or other anticonvulsant drugs is indicated in the presence of a predominant neuropathic component. Other frequently associated "adjuvant" drugs are tricyclic antidepressants or selective serotonin reuptake inhibitors, sedatives, corticosteroids, or drugs used to relieve side effects. Laxatives or peristalsis enhancers (e.g. senna compounds) are almost always necessary with opioids, and more than 50% of patients will need an anti-emetic. Bi-phosphonates, such as zoledronic acid or

pamidronate, increase the analgesic effect in case of bone metastasis.

Breakthrough pain needs rescue doses of drugs, such as NSAIDs or morphine (subcutaneous or oral). Transmucosal fentanyl is very useful for this kind of incidental pain due to its pharmacokinetics (time of action very short: 3-4 minutes) [9]; independent of the dosage of opioid already utilized, treatment should start with lower dosage (200 µg) and then be increased depending on the clinical response.

Many individual variables play a role in optimal pain control with opioids; in this context, the substitution of one strong opioid with another is sometimes necessary. The aims of opioid switching are to avoid or lower side effects, ameliorate the analgesic power and decrease the tolerance effect. Recent recommendations [10] indicate appropriate options: a) a conversion ratio of 100:1 between oral morphine and transdermal fentanyl, b) a conversion ratio of 75:1 between oral morphine and transdermal buprenorphine, c) a conversion ratio of 5:1 between oral morphine and oral hydromorphone and d) a conversion ratio of 1.5:1 between oral morphine and oral oxycodone.

The response to treatment must be monitored to ensure that the benefits of the treatment are maximized and the adverse effects minimized (Table 1). In a particular setting, opioids can be administered through epidural or intrathecal catheters with low-rate infusion-pumps. This modality allows so-called "patient-controlled analgesia" (self-administration of drug bolus for breakthrough pain) [5]. Recently, a new strong opioid (tapentadol) has appeared on the market for the treatment of severe chronic pain [11]. Tapentadol combines µ-opioid receptor agonism and noradrenaline reuptake inhibition in a single molecule, with both mechanisms contributing to its analgesic effects. Interestingly, µ-opioid agonism is primarily responsible for analgesia in acute pain whereas noradrenaline reuptake inhibition is more important in chronic pain. The presence of more than one causative mechanism is frequent in pancreatic cancer-related pain and, therefore, there is great potential for tapentadol in this field.

Conclusions

Pain treatment in pancreatic cancer is difficult. It is mandatory to control symptoms in the very early phase

Table 1. The most common side effects of opioids and their treatment.

Side effect	Treatment
Nausea	Haloperidol
Constipation	Laxatives, enemas, hydration
Vomiting	Haloperidol, opioid dosage decrease
Sedation	Opioid dosage decrease
Mental confusion	Opioid dosage decrease
Urinary problems	Opioid dosage decrease
Pruritus	Anti-histamines, opioid dosage decrease
Dryness of mouth	Hydration

and to frequently monitor the efficacy of the treatment. Complications encountered during the course of the disease should be treated promptly, when possible, as they negatively influence the analgesic response. At the moment, drug treatment still plays a crucial role in pain control for patients suffering from pancreatic cancer. Management should be focused on avoiding or lowering pain intensity, preventing and/or reducing side effects of the analgesics and finally improving the quality of life. To this end, understanding the causes of pain, performing a comprehensive evaluation, optimizing drug treatment and understanding the clinical response are the main aspects. The basic rules for analgesic treatment include respecting the scheduled time of administration, avoidance of “on-demand” doses, and careful consideration of drug-kinetic properties of the single molecules. The right dosage is that which gives full analgesia with the fewest side effects and it should not be considered a chimera but a reliable target in clinical practice.

Conflicts of interests The author has no potential conflicts of interests

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