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Cancer Pain Management—New Therapies

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Abstract

Purpose of Review Despite the rapid advance in anti-cancer treatment in recent years, the treatment to cancer-related pain remains largely unchanged. One systemic review has shown that approximately 32% of patient with cancer-related pain were undertreated. While in patients responding to strong opioids, long-term use of opioids will lead to many undesired side effects such as constipation, tolerance, and addiction. The goals of this review are to re visit the current algorism of cancer pain management and bring attention to the emerging interventional pain management techniques.

Recent Findings Peripheral nerve stimulation (PNS) has been successfully used to treat certain types of chronic non-cancer pain with long-term analgesic effect. PNS has also brought some promising results in treating localized cancer-related pain in a pilot study.

Summary More studies are needed to advance the novel and safe treatment of cancer-related pain. Incorporating interventional techniques such as PNS properly can optimize the current treatment strategy and improve outcomes.

Keywords Cancer-related pain · Interventions · Neuromodulation · Peripheral nerve stimulation

Introduction

Cancer patients often experience pain during their anti-cancer treatment. A systemic review revealed that 33% patients report pain when they receive curative cancer treatment, 59% patients report pain while receiving ongoing cancer treatment, and 64% patients report pain when their cancer is advanced or terminal [1]. While novel therapies to cancer have been developed rapidly in recent years, the overall management of cancer-related pain has been largely unchanged. The WHO three-step analgesic ladder has served as the guideline of cancer-related pain treatment since 1986. The original algorism was based solely on the pharmacological reagents including opioid and non-opioid medications. The revised algorism added "Invasive and Minimally Invasive Treatments" as step 4 when all pharmacological options fail [2•]. This analgesic ladder has simplified the cancer-related pain management so it could be easily used even by non-pain medicine experts. However, the management of cancer-related pain is considered far more complex than the simplified 3-tiered "analgesic ladder" [3••], and the efficacy of this algorism is debatable [4]. Despite the strict adherence to the WHO guideline, studies have shown that undertreatment of pain in cancer patient is very common [5, 6].

Goals and Strategies of Cancer-Related Pain Management

The "5As" of cancer-related pain management outcomes have been endorsed by the National Comprehensive Cancer Network (NCCN) in the recently revised guideline of adult cancer pain management (Version 3.2019) [3••]. The goals of pain management in cancer patients are to optimize outcomes in the following five dimensions:

Analgesia: optimize analgesia (pain relief)
Activities: optimize activities of daily living (psychosocial functioning)
Adverse effects: minimize adverse effects

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Aberrant drug taking: avoid aberrant drug taking (addiction-related outcomes)
Affect: relationship between pain and mood

Inadequate analgesia with or without unbearable adverse effects often triggers negative activities/affect, and increase the risk of developing aberrant drug taking behavior. A better outcome is achieved when the multidisciplinary care team including oncologist, pain management physician, surgeon, psychologist/psychiatrist, and PT/OT work closely with patients to personalize the treatment plan and find a balance among the "5As." A multimodal treatment approach which incorporates a judicious use of pharmacological agents, interventional therapies, psychological therapies, physiotherapy, and alternative remedies, is often required.

Pharmacological treatment options for cancer-related pain have been summarized in recently published guidelines from both European Society for Medical Oncology (ESMO) [7••] and NCCN [3••]. These guidelines are in line with the principle of WHO "three-step ladder" algorism. The regimen starts from the lowest step including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen and moves up towards the weak or strong opioids, depending on the patient's pain. In practice, the use of NSAIDS and acetaminophen is limited in treating cancer-related pain largely due to the overlapped adverse effects with the undergoing chemotherapy (e.g., kidney or liver toxicity). In addition, because of their antipyretic effect, they are often avoided in the fear of masking the superimposed infection when patients are receiving continuous chemotherapy. Weak opioids such as tramadol and codeine are still listed in both guidelines, but their value in treating cancer-related pain is minimal. Systemic reviews only found limited evidence of using either of them to treat cancer pain [8, 9]. It has been suggested that the provider should skip weak opioids and initiate strong opioids when treating moderate pain. Opioids have been the main stream of treating cancer-related pain for decades, but the amount and quality of evidence around the use of opioids for cancer pain are surprisingly low. A review of Cochrane reviews has found that reviews on buprenorphine, hydromorphone, methadone, tapentadol, and oxycodone did not show confirmatory information about the primary outcome which is the efficacy for adequate pain relief when those medications were used. Even reviews on oral morphine and transdermal fentanyl reported that the majority of patients had adequate pain relief with careful titration, the conclusion is not solid because the quality of the studies was very poor [10]. As a consequence, non-pharmacological procedures were added to the ladder as the fourth step to combine with the use of opioids or other medications. These interventional and minimally invasive procedures include epidural analgesia, intrathecal administration of analgesic and local anesthetic drugs, neurosurgical procedures (e.g., cordotomy), neuromodulation strategies (e.g., brain stimulators, spinal cord stimulation), nerve blocks, ablative procedures (with chemical or thermal), vertebral augmentation, as well as palliation radiotherapy [2•]. No consensus of when those interventional procedures should be incorporated into the regimen of treatment has been reached so far.

Targeting Peripheral Nerve to Treat Cancer-related Pain

Peripheral nerve block guided by imaging such as ultrasound is routinely used for postoperative pain control for certain types of surgeries. For chronic pain associated with cancer, a diagnostic nerve block is typically performed first to identify the correct nerve(s). If a positive response (> 50% pain relief) is obtained after nerve block, thermal or chemical ablation may be followed in the hope of achieving possible long-term effect for pain relief. This approach can be used to treat chronic cancer-related pain located in extremities or trunk. A summary of the application and techniques to target different nerves has been described by Candido et al. [11]. While these regional anesthesia techniques have been demonstrated to show promising effects such that it can relieve intractable or even difficult to treat cancer related pain [12], there are some disadvantages. First, the effect of most of the blocks or even ablation is only temporary. It varies from several days to several weeks, rarely several months [12]. Second, ablation of some nerves can pose significant risks or side effects even the diagnostic block may initially have provided excellent pain relief. For example, ablation of nerves with mixed sensory and motor functions may cause significant negative impact on limb mobilization.

Peripheral nerve stimulation (PNS) to treat chronic pain was first described by Wall and Sweet in 1967. They found that a number of patients with chronic refractory postamputation pain responded surprisingly well to electric stimulation through implanted electrodes next to the major nerve innervating the affected limb [13]. But this treatment option was not used widely due to the complexity of the open implant technique and relatively high rate of complications such as lead migration, postoperative pain, and loss of efficacy over time. Later, a percutaneous PNS implant technique was introduced by Weiner and Reed, which significantly lowered the invasiveness of the procedure [14]. In recent years, the wide availability and use of ultrasound have made it possible to guide the placement of stimulating leads near deeper targets with real-time imaging. These advances in technologies have greatly promoted the use of percutaneous PNS implantation in chronic pain management. Currently, PNS is indicated for a variety of chronic pain conditions including neuropathic pain such as post-traumatic/postsurgical neuralgia, occipital neuralgia or cervicogenic

occipital pain, genitofemoral neuralgia, postherpetic neuralgia, coccygodynia, complex regional pain syndrome, chronic headaches such as cephalgias, migraine, and cluster headaches [15].

The large-scale randomized clinical trial of PNS is still lacking, largely due to the challenge of having true "blinded" group since the stimulation often induces paresthesia. But the existing data including retrospective studies and case reports has shown overall promising outcome of using PNS to treat chronic non-cancer pain [16•, 17]. For cancer-related pain, a pilot study by Mainkar et al. has provided exciting data with PNS [18••]. In the study, they found seven out of 12 patients with cancer-related pain responded well to PNS with at least 50% pain relief. The location of pain ranged from single limb (arm or leg) to trunk (chest wall or back). The etiology of their pain included surgery (post-mastectomy syndrome), herpes (post-herpetic neuralgia), cervical or lumbosacral radiculopathy, and single nerve neuropathy. This particular PNS device (SPRINT® PNS system, SPR Therapeutics, Cleveland, OH, USA) is not permanently implanted. The leads are removed after up to 60 days of stimulation. The striking result is that long-term pain relief was observed even after the leads were extracted. Five patients had more than 4 months of pain relief with 18 months being the longest and one patient had 6 weeks of pain relief. Similar long-term effect was observed in reports of chronic non-cancer pain patients suffering from post-amputation pain [19, 20], pain in the extremities caused by nerve entrapment [21], and chronic shoulder pain [22, 23]. Recently, Gilmore et al. have found that 67% of patients experienced significant improvement of chronic back pain for up to 12 months after the completion of 30-day treatment [24].

The foundation of PNS is the "gate control" theory outlined by Melzack and Wall in 1965 [25]. They proposed that pain perception is controlled by a gating mechanism in the spinal cord with integration of inputs from small (nociceptive) and large (non-nociceptive) fibers and spinal interneurons including inhibitory and excitatory neurons. The increased input from small fibers will "open" the gate enhancing transmission of pain signals to the brain, while the increased input from large fibers will "close" the gate, reducing pain transmission. Studies have found the imbalance between the positive and negative inputs in chronic pain status and restoring/enhancing the input from large fibers could alleviate pain [26]. The exact mechanisms of PNS is not clear, but it has been proposed that selective activation of non-nociceptive, large fibers by PNS can modulate the biochemistry of local microenvironment [27] and recondition the primary sensory cortex corresponding to the painful body area [28•].

Common complications associated with PNS implant procedure are bleeding, infection, lead migration, and lead fracture. Fortunately, with percutaneous implant technique and the design of the coiled leads, the rate of severe complications has been very low, about 0.1% for 60-day implants [29]. Because most of the PNS devices are not fully MRI compatible and cancer patients often require periodic MRI scanning, the SPRINT PNS device actually provides an extra advantage than the permanent implanted system since it is completely extracted after 60-day treatment, allowing patients to have future MRI scanning if needed.

Timing of Interventional Treatment

While mild-to-moderate pain can be successfully managed by medications, management of severe pain remains challenging. Even patients respond to strong opioids in the beginning, and the loss of efficacy due to tolerance to medications or the exaggeration of side effects from escalation of doses often halts the continuation of treatment. Some patients may prefer not taking chronic medications at all. Both ESMO and NCCN guidelines support the use of interventional treatment for severe cancer-related pain, although the timing of intervention is still debatable. Previous studies suggest that an early application of interventions could improve pain control, decrease risks for adverse effects [12], reduce the consumption of opioids and opioid-associated side effects [11], and even increase survival time in cancer patients [13]. Advanced technology has expanded the interventional options and made them safer and less invasive, thus reducing the rate of complications overall. It is reasonable to consider interventional treatment before strong opioids are initiated at the early stage of cancer-related pain management.

Conclusions

Current guidelines have setup the principle of managing cancer-related pain, but the treatment plan to individual patient has to be personalized to balance among the "5As." Combination of pharmacological and non-pharmacological interventional options can promote the optimization of management. Early application of interventional treatment may minimize or even avoid the use of strong opioids. Emerging new therapy such as peripheral nerve stimulation has shown some promising clinical outcomes. More research and studies are needed to explore the novel treatment options.

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