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John S. M. Leung *

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Research Article

Some Unconventional Modifications of Pain Management in Advanced Cancer

John S. M. Leung

St. Paul's Hospital, Hong Kong

***Corresponding Author:** John S. M. Leung, St. Paul's Hospital, Hong Kong.

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Abstract:

Pain is a common major symptom of advanced cancer and over the years numerous agents and methods have been developed for pain control. However, not all patients would respond to treatment, and of those that respond, many would develop drug resistance or intolerable side effects. This is a review of some simple unconventional agents and methods which might hopefully bring some relief to the sufferings of these unfortunate patients. These include the revival of an abandoned old drug like thalidomide, unconventional route of administration of the common paracetamol and the uncommon use of botulinum toxin, the unconventional exploitation of methylnaltrexone in conjunction with opioids, the potential of a newcomer, suzetrigine and a brief review of complementary medicine. It is hoped that judicious application of these agents might bring more relief of pain and suffering to some of the advanced cancer patients.

Keywords: cancer pain; thalidomide; rectal paracetamol; methylnaltrexone; suzetrigine

Introduction

Cancer is one of commonest severe illness afflicting mankind and pain is one of the commonest and most distressing symptoms associated with cancer. Indeed, often the suffering from pain could become so severe and uncontrollable that death might come as a welcome relief. It is a well-established duty of a health care personnel "To cure sometimes, to relieve often, to comfort always." – a saying accredited to Hippocrates and echoed by many physicians in subsequent generations.[1] However, it is common experience for a practicing physician that after exhausting all conventional methods of pain relief, the cancer patients often continue to suffer and have their quality of life severely compromised. This is a review of some personal efforts to modify conventional methods of pain relief to make them "go the extra mile."

Thalidomide[2]

Notorious for creating deformed "thalidomide babies" this is a drug that carries a taboo resulting in over half a century of condemnation. It turned out that its toxicities such as anti-inflammation, anti-angiogenesis, anti-neoplasia and immunomodulation could be repurposed to treat erythema nodosum and multiple myeloma. While newer analogs such as lenalidomide and pomalidomide were developed for stronger anti-cancer activity (and with bigger financial incentive), none could match the original drug's tranquilizing, anti-emetic and anti-neuropathic pain activity.[2] In a patient with advanced cancer, pain could come from both cancer-induced neuropathy and treatment-induced neuropathy, the latter being more pronounced with the popular taxanes and platinum compounds. Therefore, thalidomide is well-positioned to treat such pain. As a bonus, thalidomide remains one of the very few anti-cancer and analgesic agents that overcomes nausea and vomiting or even improves the appetite. However, its teratogenic effect must be impressed strongly upon the patient and the caretaker. In no way should it become accessible to people of reproductive age. It is also advisable to keep the drug at its lowest effective dose as high doses per se over prolonged periods might rarely cause neuropathy.

Opioids and anti-constipation combinations

Opioids, whether by oral, injection, or transdermal patch application is given almost universally to cancer patients in pain. But there are important problems to consider. The first is addiction, which in the case of advanced cancer might be acceptable as a necessary evil. Next come constipation and respiratory depression, which tend to amplify the various ongoing discomfort of the cancer patient.[4] A standard remedy is to use a mu-opioid receptor antagonist, naloxone, which neutralizes the constipation and hypoventilation effects without subtracting much of the analgesic effect and permits higher dosage of opioids to expedite analgesic effects.[5] The downside is that naloxone amplifies the nausea caused by opioids.

Methylnaltrexone (MNTX)[6] – adding antineoplastic effect to symptomatic palliative care

Many patients and their families find it difficult to accept palliative care, not only because of the negativity of the concept but also from practical experience of faster deterioration once the patient is put on opioids, often at increasingly high doses, and with all anti-cancer measures withdrawn. One of the immediate side-effects is constipation which could be as upsetting to the patient as the pain we set out to relieve. Another drawback is that the cancer seems to deteriorate faster with high doses of opioids. This has some plausible scientific basis as mu-opioid receptor itself is known to promote cancer growth. Available data show that in advanced cancer patients, MNTX added to their opioid analgesics not only mitigates the constipation, but also

significantly prolongs survival versus having opioids alone. For example, in pancreatic cancer, MNTX added to opioids was associated with an average survival of 76 days versus placebo plus opioid's 28 days.[6] Therefore, we can offer our patients a choice of palliative care, combining both opioids and MNTX, which not only relieves a major side effect of opioids but also positively impact on survival. This alleviates the usual demoralizing stigma of palliative care and makes the concept more acceptable to those patients who wish to fight their cancer to the very end.

Analgesic Combinations with Opioids

Another major problem with opioids is drug tolerance with prolonged use so that additional analgesics have to be recruited. The choice used to be a COX-1 inhibitor like ibuprofen, with a high incidence of gastrointestinal bleeding, or a COX-2 inhibitor like celecoxib or the injectable parecoxib, which carries a substantial burden of cardiovascular adversities.[7] There is now a tendency to use paracetamol for its unique synergism with opioids and more favorable profile of side effects.

Paracetamol,[8] – oral, intravenous, or rectal? Paracetamol, also known as acetaminophen, and sold under various brand names like Panadol, Tylenol etc., is one of the commonest drugs prescribed or sold over the counter. Its synergistic effect with opioids is now well recognized. In spite of its long history and extensive usage, its unique pharmacological molecular pathways are only being recently elucidated. A review of paracetamol has been reported earlier and here is a brief summary.[9] Paracetamol is not absorbed in the stomach but is rapidly and completely absorbed in the duodenum resulting in a unique spike-form of drug-loading on the liver. In the subsequent analysis we shall analyze how such a pattern of absorption impact upon paracetamol's metabolism in the liver, where it may go through one of four processes:

(1) Detoxication by conjugation;

(2) Conversion into an intermediate metabolite, p(para)-aminophenol, which could pass the blood-brain barrier to be processed in the brain to become a central-acting analgesic agent;

(3) Conversion of those paracetamol molecules that exceed the processing capacity of (1) and (2) into a hepatotoxic product, NAPQI (N-Acetyl-p-benzoQuinone Imine);

(4) The liver had to further detoxicate NAPQI, digging deep into its anti-oxidant reserve, and once that reserve is exhausted, liver damage sets in and the patient rapidly goes into liver failure. It is important to keep the loading of paracetamol within the detoxication capacity of the liver. Any excess loading of paracetamol from the oral-duodenal route will rapidly overwhelm the liver.

After the first-pass through the liver, the intermediate metabolite p-aminophenol will enter the systemic circulation and reach the brain, where it is able to cross the blood-brain barrier to be further converted to the active metabolite AMA-404 (N-arachidonoyl-phenolamine) which interacts with a wide range of pain-related receptors including COX1, COX2, COX3, nitric oxide synthase, T-type Ca_v 3.2 calcium channels, CB1 receptor, TRPV1 or TRPA1 receptor, KV7 potassium channels, and serotoninergic receptors. In this way, paracetamol is now considered an important central-acting analgesic.

The Rectal route may be a preferred route of giving Paracetamol[9]

It is obvious from this survey of the complicated pathways of paracetamol that the intravenous route of administration is comparatively less effective as only a small part of the administered agent would pass through the liver at any time to be converted to the intermediate p-aminophenol that the brain could utilize. On the other hand, the oral route would result in spikes of loading during which the liver's limited capacity of utilization and detoxication could be exceeded resulting in liver damage. The rectal route seems more preferable. Most of the drug would undergo a first-pass through the liver, only a small portion in the distal rectum might go directly into the systemic circulation. Since the rectal mucosa is not richly endowed with villi, its absorption is much slower than the duodenum and devoid of spike impact, so that the liver has more chance to utilize the drug by converting it into p-aminophenol, increasing its potency, and detoxicate the rest of it, reducing the risk of liver damage. For a patient suffering from advanced cancer, we need an analgesic that could be effective, without causing gastrointestinal upset or liver toxicity, and positively synergistic with ongoing opioid treatment. Paracetamol per rectum appears to fulfill these requirements.

Intercepting the afferent pain conduction pathways

The pain sensation is perceived first at the peripheral nociceptor. The impulse then passes along the sensory nerve to the dorsal root ganglion and on to the spinal cord, where it is relayed to the brain via the dorsal horn neuron and the spinothalamic tract. One of the simplest ways to relieve pain is to block the afferent conduction of the pain sensation by blocking the respective nerve supply to the site of pain origin. This could be achieved on a short-term basis by local anesthetic agents or on a long-term basis by applying a neurotoxic agent like absolute alcohol or botulinum toxin. Botulinum toxin has been successfully used in controlling the pain of the uncommon cutaneous leiomyoma by intralesional injection.[10] Alternatively, ablation of the nerve could be carried out by physical means like temperature, ultrasound, radiation or surgical transection. Such drastic measures make no distinction between pain conduction and other nerve function so that the patient will lose all feeling, movement or control of the tissue innervated by the ablated nerve.

Suzetrigine and Na_v 1.8

The voltage-gated sodium channel, Na_v 1.8 is the operational membrane protein controlling the action potential that expedites pain impulse action potential and its conduction in the peripheral nerve. Selective inhibition of Na_v 1.8 would seem a logical development of precision-driven peripheral-acting analgesia.

On January 30, 2025, Vertex Pharmaceuticals announced that one of its products, suzetrigine, had obtained FDA approval. The news was enthusiastically boosted with much rhetoric, like first truly new non-opioid analgesic agent in over 20 years and, as a Na_v 1.8 inhibitor, first agent of its class approved by the FDA.[11] In real life, the drug has only been tested as a postoperative analgesic in two types of surgery, abdominoplasty and bunionectomy.[12] It was not given longer than 14 days, nor tried extensively in pain other than in the postoperative setting.[14] Its analgesic efficacy was substantially superior to placebo but no better than the commonly used combination of an opioid (hydrocodone bitartrate) and paracetamol. For control of the chronic pain of cancer, it needs to be tried for much longer than 14 days, and to show additive, if not synergistic, analgesic value to extant agents like opioids and COX inhibitors. Given its entirely different mode of action, its addition should be at least of additive value to other established analgesics.

The use of suzetrigine is not without reservation. It is known to have adverse interactions with CYP 3A inhibitors and substrates, including common health foods such as grapefruits, caffeine and green tea extract, as well as a wide range of medicines spanning across anticancer drugs, antibiotics, antivirals, statins, anti-depressants, anti-epileptics, anticoagulants, anti-arrhythmic agents and so on.[15] This markedly limits its potential as an add-on analgesic in the common scenario of polypharmacy in advanced cancer. It would be desirable to extend the application of suzetrigine by further studies and trials. Ideally, we should further explore alternative methods with less food and drug interactions to modify the activities of Na_v 1.8 channel in the dorsal root ganglion and pain conduction fibers.

Alternative medicine and alternative attempts to reduce afferent pain signal conduction

As a major part of TCM (Traditional Chinese Medicine), acupuncture has been presented as an effective method of pain relief. However, its contribution to cancer-associated pain has been unreliable at best and totally ineffective at worst. Acupuncture carries a substantial risk of damage to internal organs, the commonest being damage to the lung with life-

threatening pneumothorax. Substituting the needle with non-invasive methods would seem a reasonable next step forward.

During the last quarter of the 20th century, Frances C.K. Mahr, an eminent TCM practitioner advocated against the use of the needle in acupuncture but use the finger tip to apply pressure on the acupoints instead.[14] The method eliminated the immediate risk of using the needle but was very much operator-dependent, and ineffective for cancer-associated pain. In fact, like many other TCM practitioners, Mahr considered cancer should primarily be managed by Western Medicine, and TCM only has a supportive role.

Transcutaneous electrical nerve stimulation (TENS)[15]

Another ancient method, rejuvenated for medical purpose is electrical stimulation. Egyptians 4000 years ago had harnessed electrogenic fish as a form of therapy. The Gate theory of afferent pain conduction provided a simple and easily understandable basis of pain conduction. At the dorsal horn of the spinal cord, the pain signal had to negotiate a "busy line" for its ascending conduction to the brain. By using additional electric stimulation to "jam" the conduction line, it was thought possible to downplay the pain conduction. However, pain conduction proved more complicated than the Gate theory, and the "busy line" concept might not be ubiquitously applicable.[16] TENS might be ineffective in some situations and even worsen the patient's suffering where there is hyperesthesia, paresthesia or allodynia. None-the-less, an extensive review in 2022 concluded that TENS is essentially effective in many, if not most, situations.[17] In the case of cancer related pain, however, the effect of TENS remains inconclusive.[18]

Modification of TENS, Hui's modification[19]

Perhaps the development of suzetrigine could shed new lights in the TENS approach. For many years, pain conduction was focused on the nerve fibers, the fast-conducting myelinated A delta fiber conducting the sharp acute pain and the slow unmyelinated C fiber conducting the dull chronic pain. For peripheral analgesia, attention was focused on intercepting these nerve fibers. Studies on suzetrigine showed that the focus of interest should be on the Na_v 1.8 channel that expedite pain conduction. Since the maximal Na_v 1.8 activities occur around the dorsal root ganglion, any local treatment would be more effective if focused on that region.

Revisiting the TENS approach in the light of analgesia by Na_v 1.8 inhibition

For the past 50 years, this author had been working with a dedicated health personnel educated and trained in both Traditional Chinese and Western Medicine, Simon SK Hui, on the modification of TENS for pain management on patients who had failed to respond to other forms of treatment including pharmaceutical products and the usual methodology of TENS. We have found that applying contact points are better than pads, two contact points are better than one and three contact points better than two (the third point acting as the "earth" contact). The instrument must be adjustable in terms of amplitude and frequency, and such adjustment should be individualized to the particular characteristics of the patient and the pain. Feedback is very important, as the strength of stimulation should be up-titrated to the maximal level that the patient could tolerate without discomfort. Expertise with acupuncture and acupoints bears no relevance to positioning the sites of electrical contact. On the other hand, stimulation is best directed according to the surface anatomy of the spinal nerve and dorsal root ganglion. In the case of a thoracic spinal nerve the best site would be along the paravertebral region at the posterior end of the intercostal space (or the equivalent site outside the thoracic region) as the spinal nerve trunk enters the spinal canal through the intervertebral foramen. Coincidentally, that would also make it rather close to the dorsal root ganglion, site of maximal Na_v 1.8 activity. Once we formulated this modification of TENS (long before our knowledge of Na_v 1.8) we began to obtain more consistent success among some 27 patients including three cancer patients. Unfortunately, most patients happened to be local celebrities and preferred to maintain their privacy even after deidentification. In any case, the scale of this study is too small and the data collected were limited and incomplete. It will require more extensive, stringently planned, and prospective, randomized, placebo-controlled studies to established its value.

Summary and conclusion

In this brief review of pain treatment in advanced cancer a number of agents, both old and new, have been brought up and revived or modified. They include

1. Thalidomide has been notorious for producing a vast number of deformed babes and condemned to obscurity for over half a century. Yet, it could provide considerable comfort to the patient including ameliorating nausea, tranquilization, analgesia especially for neuropathic pain.
2. Methylnaltrexone (MNTX) which enables the continuation of the most powerful analgesic – opioids by correcting the opioid-induced constipation.
3. Paracetamol, long considered a moderate non-selective COX inhibitor is now found to be more of a central-acting analgesic, highly synergistic with opioids with which it forms a strong analgesic partnership. We found that by using the rectal route of administering paracetamol we can bring out its best efficacy.
4. We have taken note of the newly developed and FDA-approved analgesic, suzetrigine, first in the class of Na_v 1.8 inhibitor and pleaded for further studies to extend its use in cancer patients.
5. We have developed modifications of the Transcutaneous Electrical Nerve Stimulations for enhanced efficacy on pain-control in the advanced cancer patient. Recent discovery of the afferent conduction of the pain impulse via the function of the voltage-gated sodium channel lend theoretical support to our modification.
6. As both thalidomide and MNTX possess some genuine anticancer properties we can now honestly remove the negative and demoralizing stigma of palliative care and reassure the patient that we have only reorganized the treatment with more emphasis on pain relief without abandoning the original theme of fighting the cancer.

In conclusion, a few suggestions have been outlined for the control of cancer-associated pain which are outside the usual conventional practice. Hopefully these suggestions might help to alleviate the pain at least in some cancer patients who fail to respond to the conventional management.

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