Current strategies for pain control

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Summary

Pain is the most feared symptom for patients diagnosed with cancer. Although our understanding of cancer pain and its management has greatly improved in the past decade, an unacceptably large proportion of patients still do not receive adequate pain relief. Before commencing any form of treatment, patients must receive a thorough assessment in order to define the pain, causes and severity. The recommendations for progressing a patient from step 2 to step 3 of the WHO analgesic ladder are discussed here as well as the choice of strong opioid substitution. An overview of the benefits of considering alternative routes of administering strong opioids, such as the transdermal delivery of fentanyl (TTS fentanyl), and the use of opioid substitution in patients intolerant to the adverse effects of morphine are also included. Finally, newer approaches to relieving refractory pain, such as neuropathic and bone pain, are considered.

Key words: non-opioid-responsive pain, opioid choices, opioid rotation, patient assessment, TTS fentanyl

Introduction

Severe demoralising pain is the symptom most feared by cancer patients. The World Health Organization (WHO) cancer pain relief programme [1] has contributed significantly towards the progression of pain relief for cancer patients [2]. Nevertheless, even when the WHO analgesic recommendations are used as a guideline to the treatment of cancer pain, around one-fifth of patients still receive inadequate pain relief [3].

Patient assessment

Treatment of cancer pain requires as rigorous an approach as treatment of the disease itself. It is important to carry out a thorough assessment of the patient in order that the most appropriate pain relief can be administered. Assessment should involve defining the type and cause of the pain or pains, compiling a detailed drug history for the patient and carrying out a physical examination.

Cancer pain used to be thought of as a simple symptom, but is now seen as collection of pain syndromes which can vary and co-exist during the progression of the malignancy. Some pains may be acute, such as following surgery or when a bone is fractured, but the overall experience is of a chronic pain complex [4]. The first step in managing cancer pain must therefore be to define which cancer pain syndrome the patient is experiencing [5]. A physical examination of the patient can provide further information about the pain, for example, radiating pain may implicate nerve root compression and the use of nerve blocks may be required for complete alleviation. Finally, a detailed drug history should be taken, particularly when a patient has previously seen several doctors. This will ensure that drugs can be prescribed in accordance with the patient's prior responses, and any adverse effects which may have been experienced.

Moving up the analgesic ladder

If pain control is inadequate with weak opioids (step 2 of the WHO analgesic ladder) the treatment should be progressed to a strong opioid (step 3 of the analgesic ladder) [1]. The recommended approach is to titrate with instant-release morphine, either as tablets or in solution, to define the correct dose of strong opioid needed to control the pain. The four-hour half-life of instant-release morphine makes it ideal for use during this initial titration phase; the patient's response can be quickly monitored and titration is usually complete after two or three days [6]. Instant-release oral morphine should also be used as rescue medication for occasional breakthrough pain and if the patient’s pain destabilises as a result of a major event, such as a bone fracture.

Once the dose has been titrated using instant-release morphine and the patient has achieved stable pain control, a slow-release formulation may be substituted. The gold standard of treatment until recently has been slow-release morphine, available in 12- and 24-hour preparations. Many patients are more accepting of slow-release formulations because the longer half-life means that the dosing frequency is reduced compared with instant-release morphine.
In some instances, it may be possible to move the patient straight from a weak opioid to a long-acting opioid, avoiding the titration period. This method is not usually recommended because the slow-release formulations take some time to build up and toxicities may not be immediately apparent [6]. However, for patients likely to require low doses of strong opioids, this strategy enables them to benefit immediately from the convenience of long-acting formulations. Research is urgently needed to clarify the role of titration versus direct transfer to slow-release opioids.

Strong opioid alternatives to morphine

Morphine is the strong opioid designated for step 3 of the original WHO analgesic ladder and has been regarded as the gold standard in cancer pain treatment for a number of years [5]. With the development of newer strong opioids, we now have a wider treatment choice. In addition to morphine, five strong opioids are currently available for use in cancer pain treatment – methadone, oxycodone, hydromorphone, levorphanol and fentanyl [4].

Methadone has been recommended in the past as a second-line drug for patients already exposed to opioids [1]. Although its wide availability and relatively low cost make it a drug of choice for cancer pain [7], methadone is often viewed negatively by clinicians and some patients who think of it as a drug used to treat addicts [4]. It has a much longer half-life than morphine which may lead to build-up of toxicity in elderly patients. Oxycodone is most commonly used to treat moderate-to-severe pain in step 2 of the analgesic ladder [4]. Preliminary pharmacokinetic studies suggest that oxycodone has a longer analgesic action than morphine and it may have a more acceptable side effect profile than morphine [8–11], which could lead to a broader use of this drug.

To date, hydromorphone has been shown to produce excellent analgesia and is reported to be associated with a reduced incidence of side effects compared with morphine [12]. However, because of the lack of direct comparative trials with morphine or other opioids, its place in the treatment of cancer pain still needs to be fully established [4].

Leverorphanol is a synthetic opioid often used as a second-line treatment for cancer pain in patients who cannot tolerate morphine [4]. Its use remains limited because comparative studies of its side effect profile have not yet been conducted [4].

Fentanyl, a synthetic opioid, has been available for over two decades [13]. It is now available in a transdermal delivery system, which has been used to treat pain effectively in cancer patients [14–16]. Transdermal fentanyl (TTS fentanyl) combines a strong opioid with a 72-hour release profile, providing sustained, effective pain relief [13].

These alternatives to morphine offer the patient additional benefits. Substitution by an alternative opioid may improve a patient’s pain control or, more importantly, help to reduce opioid-related side effects such as constipation, sedation and cognitive impairment [17]. Clinicians caring for cancer patients need to become familiar with the new concept of ‘opioid rotation’, or better ‘opioid substitution’ to give patients the best balance between efficacy and toxicity.

Uncontrolled studies of TTS fentanyl have indicated that this drug may have an improved side effect profile compared with morphine [16,18]. The results of a recent multicentre, open, randomised, crossover trial have added strength to these findings [19]. Patients (n = 202) from 44 palliative care centres in the UK who were already using slow-release morphine were randomised to receive either slow-release morphine or TTS fentanyl. After 15 days the treatment groups were crossed over; a total of 110 patients completed the study. Rescue medication was instant-release morphine in both arms, and patients were encouraged to use this freely for breakthrough pain. Pain control was consequently equally as good in both treatment groups. However, during the TTS fentanyl phase patients reported significantly less constipation (P < 0.001) and nausea (P = 0.04) as assessed using the European Organization for Research and Treatment of Cancer core questionnaire for quality of life (EORTC QLQ-C30). Patient diaries and other measures also revealed that TTS fentanyl was associated with significantly less sedation by day and night (shorter sleep duration) and increased convenience compared with morphine (Table 1). Overall, 54% of patients preferred TTS fentanyl, 36% morphine and 10% did not distinguish between the two treatments. It was interesting in this study that overall quality of life and psychological functioning were the same in both arms, indicating that these issues are probably deeper than symptom control and side effects.

The clinical dose-effect relationship of opioids does not have a ceiling effect; the upper dose limit is defined by toxicity [18]. Many patients are intolerant to the side effects of morphine, particularly sedation, impaired cognition and nausea [17]. Whatever the cause of toxicity, there is increasing evidence to suggest that patients may benefit by substituting morphine with another strong

<table>
<thead>
<tr>
<th>Which medication …</th>
<th>TTS</th>
<th>SRM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>… caused less interruption of daily activities?</td>
<td>55%</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>… caused less interruption of family/carer’s activities?</td>
<td>49%</td>
<td>22%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>… was more convenient to take?</td>
<td>58%</td>
<td>22%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>… permitted a better night’s sleep?</td>
<td>31%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td>… relieved pain more effectively?</td>
<td>35%</td>
<td>29%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: TTS – transdermal fentanyl; SRM – slow-release morphine; NS – not statistically significant.
opioid. In a retrospective analysis conducted at the Palliative Care Unit in Edmonton General Hospital, Alberta, Canada, 80 of 191 patients underwent so-called ‘opioid rotation’ because they were experiencing cognitive failure, hallucinations, myoclonus, nausea, local toxicity or lack of pain control [17]. Overall, these leading symptoms improved in 73% (P < 0.01) of patients after opioid rotation; Table 2 shows the improvements in individual symptoms. Opioid substitution by equianalgesic doses of a different opioid can relieve some symptoms of opioid toxicity and may improve the quality of pain control. Although most experience with substitution has been reported with methadone and hydromorphone, it is likely that TTS fentanyl could also become a drug of choice in this setting since it has been shown to be associated with fewer reports of nausea, constipation and daytime drowsiness than other opioids [19]. These findings emphasise the need for enlarging the standard armamentarium for the relief of cancer pain.

### Opioid alternatives

Opioid non-responsive pain is defined as “pain that is inadequately relieved by opioid analgesics given in a dose that causes intolerable side effects despite routine measures to control them” [20]. Under these circumstances, alternative strategies for pain relief should be considered. The two most difficult types of cancer pain to control are neuropathic pain and bone pain [21].

Neuropathic pain accounts for 10%–20% of refractory cancer pain, and may be only partially responsive to opioids [21]. Once the chosen opioid has been titrated to a maximally tolerated dose, adjuvant drugs, such as antidepressants, anticonvulsants and membrane stabilising drugs (e.g., the anti-arrhythmics mexiletine and flecainide), can be added to the treatment regimen [22].

If pain control is still inadequate, non-pharmacological treatments such as selective nerve block could be considered for specific types of pain [21]; for example, coeliac plexus block for pancreatic and hepatic pain and trigeminal nerve block for facial malignant pain.

More recently, accumulating knowledge of how pain is transmitted and modified in the spinal cord has revealed that N-methyl-D-aspartate (NMDA) receptors play a very active role in aggravating chronic pain [23] and that NMDA receptor antagonists may be used to block this [24]. Despite a lack of large, well-controlled clinical trials, there is much evidence from smaller series that ketamine, an NMDA receptor antagonist, is an effective treatment for chronic refractory neuropathic pain [23].

Skeletal metastases, and the resulting bone pain, affect a large proportion of patients with advanced cancer, particularly those with cancer of the breast, prostate or lung [25]. Short courses of palliative radiotherapy and intravenous strontium-89 have both been proven efficacious in the treatment of bone pain. The results of recent trials have also shown that bisphosphonates, originally developed to control hypercalcaemia, can relieve pain from bone metastases [26], prevent long-term complications such as fractures [27], and slow down the time to progressive bone disease [28].

### Conclusions

Control of cancer-related pain is a key element of ensuring that cancer patients achieve an acceptable quality of life and a modern systematic approach should be offered to all patients, regardless of the stage of their disease. The first step in controlling pain is to define its cause and severity. Only then can a rational choice of treatment be implemented. Cancer pain is not necessarily uniform, its aetiology and intensity can fluctuate during the disease. Thus, once an initial course of action has been decided upon, there should be close monitoring to ensure that the treatment regimen is continually adapted to meet the changing needs of the patient. The WHO three step approach is adequate for the majority of cases, using the principle of titrating with instant-release morphine before starting one of the sustained-release opioids, for severe pain. Clinicians should be fully aware of the advantages and limitations of the increasing range of opioid and non-opioid drugs and non-pharmacological treatment options available. Physicians and patients should both be able to make informed choices between treatments based on knowledge of efficacy, side-effects and convenience.

### References


### Table 2. Improvement of leading symptoms after first opioid substitution. Results of a retrospective analysis of the charts of 80/191 patients who underwent opioid rotation at the Edmonton General Hospital, Alberta, Canada [20].

<table>
<thead>
<tr>
<th>Symptom of opioid toxicity</th>
<th>No. of patients</th>
<th>% Improved</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive failure</td>
<td>42</td>
<td>69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>15</td>
<td>66</td>
<td>NS</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>10</td>
<td>70</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Local toxicity</td>
<td>1</td>
<td>100</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS – not statistically significant.


23. Luuczak J, Dickenson AH, Kotliiska-Lemieszek A. The role of ketamine, an NMDA receptor antagonist, in the management of pain. Prog Pall Care 1995; 3: 127-34.


