available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Management of Cancer Pain: Basic Principles and Neuropathic Cancer Pain

B. Laird[a,*], *L. Colvin*[b], *M. Fallon*[a]

[a]*Institute of Genetics and Molecular Medicine, Edinburgh Cancer Research Centre (CRUK), Western General Hospital, Edinburgh EH4 2XR, UK*
[b]*Department of Anaesthesia, Critical Care & Pain Medicine, Edinburgh Cancer Research Centre (CRUK), Western General Hospital, Edinburgh EH4 2XR, UK*

ARTICLE INFO

Article history:
Received 10 March 2008
Accepted 11 March 2008
Available online 23 April 2008

Keywords:
Cancer
Oncology
Pain
Neuropathic
Management

ABSTRACT

Pain is one of the commonest symptoms in patients with cancer occurring in as many as 90% of patients during their illness. Pain is a complex phenomenon, which can be exacerbated by numerous other factors. This paper discusses the common strategies for the management of cancer pain in general and also neuropathic cancer pain. Using the World Health Organisation (WHO) analgesic ladder for cancer pain relief, 80% of cancer pain can usually be controlled. It follows therefore that 20% of cancer pain can be difficult to control. Neuropathic cancer pain is often in this category and the use of adjuvant analgesics such as amitriptyline and gabapentin is important. Optimum cancer pain control is achieved by integrating standard analgesic approaches during tumouricidal therapy or any other active cancer treatment.

1. Introduction

Pain is one of the most common symptoms in patients with cancer. A single-point prevalence study conducted by the International Association for the Study of Pain (IASP) concluded that 90% of patients with cancer experience pain at some point during their illness.[1]

Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[2] This is clearly a complex multi-factorial phenomenon. The relationship between physical pain and emotional distress is complicated. Our previous models were clearly oversimplified where psychological issues were considered to increase the distress associated with pain and therefore the perceived pain. Our current understanding of the mechanisms of pain has clarified that pain pathways are linked directly to and modified by both midbrain and cortical (anxiety/depression/sleeplessness/fear) pathways. The net result is a direct, positive effect on pain intensity in the absence of anxiety, fear and depression or a direct negative effect in the presence of the former resulting in an increase in pain (Fig. 1).

2. Common approaches to the management of cancer pain

2.1. *WHO analgesic ladder*

The principles of pharmacological pain management should usually follow those set out in the World Health Organisation (WHO) analgesic ladder for cancer pain relief.[3] It has been shown that in specialist units, that the WHO guidelines relieve 80% of cancer pain.[4]

The WHO ladder is divided into three steps (See Fig. 2).

Step One: Non-Opioid Analgesia - The first step is the use of non-opioid analgesia. This includes paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs).

* Corresponding author: Tel.: +00441317773529; fax: +01317773520.
E-mail address: barry.laird@ed.ac.uk (B. Laird).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.03.022

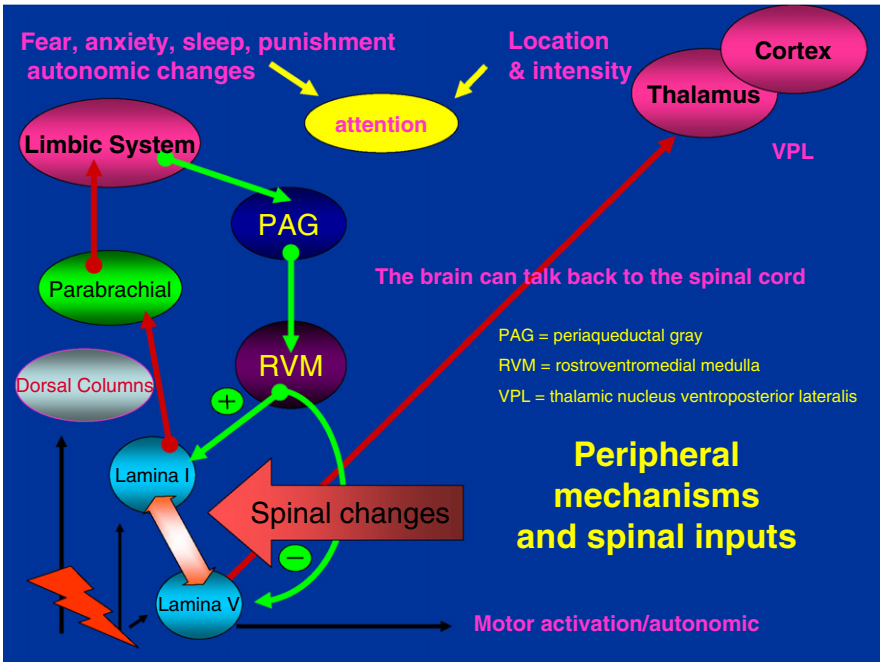

Fig. 1 – Integration of pain and distress. Courtesy of Professor Anthony Dickenson, UCL, London.

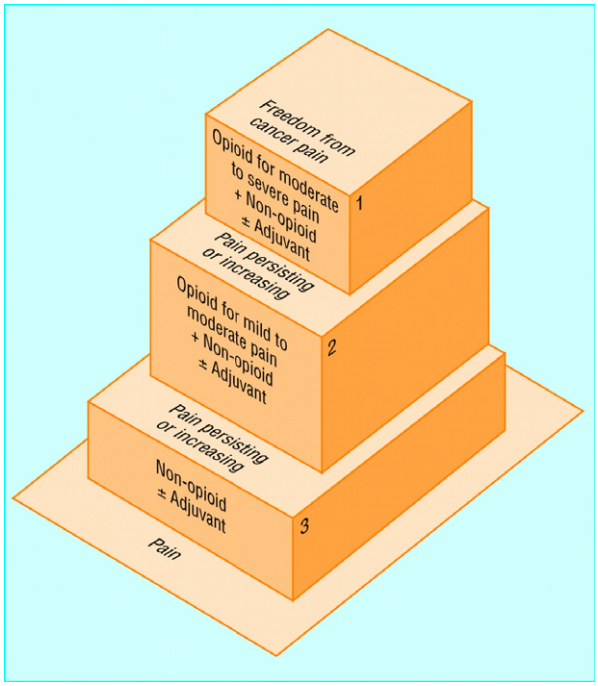

Fig. 2 – World Health Organisation Analgesic Ladder for Cancer Pain Relief.

Step Two: Weak Opioids - There are several weak opioids available, however codeine 60 mg 6-hourly is the most commonly used in combination with paracetamol 1 g 6-hourly.

Step Three: Strong Opioids - Morphine remains the gold standard and usually is the opioid of choice. In the initial stages of opioid titration, immediate release morphine should be prescribed (usually 5-10 mg orally, 4-hourly, and the same dose allowed for breakthrough pain). Analgesic requirements can then be assessed and, if appropriate, controlled release preparations (12 or 24 hourly) can be commenced.

Oxycodone, fentanyl, hydromorphone, buprenorphine and methadone are alternative strong opioids to morphine. Alternatives are usually tried where patients have unacceptable adverse effects with morphine or an alternative route is desired with a transdermal preparation such as fentanyl or buprenorphine.

Adjuvant Analgesics - An adjuvant analgesic is a drug whose primary indication is for something other than pain, but has an analgesic effect in certain painful conditions.[5] Not only are adjuvant analgesics important per se, but they have an opioid-sparing effect.

Adjuvant analgesics can be added at any stage of the WHO ladder and are chosen according to the underlying pathophysiology of the pain (See Table 1).

3. Difficult cancer pain

The two areas of difficult to control cancer pain are cancer-induced bone pain (CIBP) and neuropathic pain. In reality, most complex cancer pain has more than one component, however there is usually a dominant component. The underlying mechanisms of neuropathic pain, and mechanisms and management of CIBP, are covered elsewhere in this special issue.

4. Clinical management of neuropathic cancer pain

Neuropathic pain can be poorly responsive to opioids because higher doses are often required which increases the likelihood of unacceptable side-effects and therefore limits dose

Table 1 – Adjuvant analgesics[a]

Drug	Dosage	Indications	Side-effects[b]
NSAIDs e.g. Diclofenac (or COX-2 NSAID if high risk of GI side-effects)	50 mg oral 8-hourly (SR 75 mg 12-hourly) 100 mg per rectum once a day	Bone metastases, soft tissue infiltration, liver pain, inflammatory pain	Gastric irritation and bleeding, fluid retention, headache; caution in renal impairment
Steroids e.g. dexamethasone	8-16 mg per day; use morning; titrate down to lowest dose which controls pain	Raised intracranial pressure, nerve compression, soft tissue infiltration, liver pain	Gastric irritation if used together with NSAID, fluid retention, confusion, Cushingoid appearance, candidiasis, hyperglycaemia
Gabapentin[a]	100-300 mg nocte (starting dose) (titrate to 600 mg 8-hourly; may need higher dose)	Nerve pain of any aetiology	Mild sedation, tremor, confusion
Amitriptyline (evidence for all tricyclics)[a]	25 mg nocte (starting dose) 10 mg nocte (elderly)	Nerve pain of any aetiology	Sedation, dizziness, confusion, dry mouth, constipation, urinary retention; avoid in cardiac disease
Carbamazepine (evidence for all anticonvulsants)[a]	100-200 mg nocte (starting dose)	Nerve pain of any aetiology	Vertigo, sedation, constipation, rash

a Drugs with a primary indication other than pain, but analgesic when used as above
b In the elderly all drugs can cause confusion.

escalation.[6–8] Some studies have suggested that 50% of all difficult to manage cancer pain is neuropathic.[1,9] Uncontrolled neuropathic pain is associated with anxiety, depression and reduced quality of life.[10,11]

The widely-used adjuvant analgesics are an important part of our neuropathic pain armamentarium; the choice of adjuvant analgesic is not based on potency superiority as all have a number-needed-to-treat of about three (NNT = 3).[12] This means that of every three patients treated, one is likely to get pain relief. Choice is based on an individual's likely sensitivity to a specific side-effect profile, such as postural hypotension with amitriptyline.

An adjuvant analgesic for neuropathic pain will generally be prescribed early.

4.1. *Anticonvulsants*

Currently gabapentin and pregabalin are commonly used as adjuvant analgesics. To date they have not been shown to have a lower number-needed-to-treat (NNT) than the older anticonvulsants .[12]

4.2. *Antidepressants*

A Cochrane review provided a valuable summary of the current evidence for the use of antidepressants in non-malignant neuropathic pain.[13] Tricyclic antidepressants have been shown to provide at least moderate pain relief (NNT = 3.6). More recently, data from three studies have supported the use of Venlafaxine (NNT = 3.1). A newer dual uptake inhibitor, Duloxetine, also shows early evidence of being useful.[13] At present there is insufficient evidence to support the use of selective serotonin reuptake inhibitors (SSRI).

The advantage of Venlafaxine and Duloxetine is that they can serve a useful therapeutic role for clinical depression. Venlafaxine however does appear to have more side-effects than Duloxetine.

4.3. *Others treatments*

Ketamine- The N-methyl-d-aspartate (NMDA) receptors within the spinal cord have been shown to have a significant role in the pathophysiology of chronic neuropathic pain. Ketamine is an NMDA antagonist which has been studied in neuropathic pain and evidence exists for its use, either orally or parenterally.[14,15]

Topical Lignocaine – good evidence exists for use in patients with post-herpetic neuralgia.[12] It is available either as a patch or a 5% topical gel. It has a low risk of side-effects and is effective in approximately one in four patients who have localized, peripheral neuropathic pain. It can be used either alone or in combination with other medications. Lidocaine patches have been used in cancer-related neuropathic pain where allodynia (sensitivity to light touch) exists.[7]

4.4. *Peripheral neuropathy*

Peripheral neuropathies can be a serious side-effect to various chemotherapies, and can result in a dose reduction or cessation of treatment. Management is based on the adjuvant drugs (antidepressants, anticonvulsants, topical agents and ketamine) outlined above.

While most patients have a natural resolution of neuropathy, a few have persistent, troublesome problems (Table 2).

4.5. *Anaesthetic Interventions*

It has to be remembered that the WHO analgesic ladder is intended to be used alongside other strategies such as chemotherapy, radiotherapy and non-pharmacological pain treatments, such as TENS and physiotherapy. Clearly, a small number of patients will need anaesthetic interventions and while they can be considered as Step 4 of the analgesic ladder, it is more useful to consider this need at any appropriate

Table 2 – Neuropathies associated with specific chemotherapies and biological therapies

Chemotherapy	Type of neuropathy (incidence)	Onset time (coasting)	Duration/ recovery	Other differences
Cisplatin (carboplatin)	chronic	c. 1 month (+)	Some resolution in 80% over months/years	Carboplatin less CIPN
Oxaliplatin	Acute (90%) and chronic	Acute: hours Chronic: c. 1 month (+)	Acute: Chronic: as cisplatin	Acute pain in up to 90%, cold induced
Vincristine (vinblastine)	Chronic (30% severe)	Peak 2-3 weeks (+)	Some recovery 1-3 months, longer recovery into years	Paraesthesias common, vinblastine less CIPN
Paclitaxel (docetaxel)	Chronic	Within days (+)	@6/12 19% complete recovery, 25% no recovery	More CIPN with more frequent dosing; docetaxel less CIPN
Bortezomib (Velcade®)	Chronic (35%)		At 2 y 71% some recovery	
Thalidomide	Chronic	Any time (+)	Recovery less likely	No cumulative dose response, daily dose

Table 3 – Factors affecting choice of spinal route of delivery

Epidural	Intrathecal
Procedural	
• Simple procedure—local anaesthetic with or without sedation	• Sedation or general anaesthesia usually required
• Fixation can be difficult	• Deep fixation at time of insertion
• Catheters not designed for long term use	• Silastic catheter designed for long term use
• Drug spread may be limited, especially if there is tumour in the epidural space, or scarring related to radiotherapy	• Drug spreads within CSF, unless obstruction to flow; lipid solubility determines degree of spread
• Safety—catheter migration to intrathecal space delivering potential overdose	• Safety—catheter can only migrate out of intrathecal space
Prognosis	
Short term use:	Longer term use:
• Limited prognosis	• Several different options—for example, external or fully implantable
• Other definitive treatment planned—for example, radiotherapy	
• Trial for intrathecal line	

point. The majority of evidence is for celiac plexus block for upper abdominal pain and for spinal analgesia, either epidural or intrathecal which is of particular use in pelvic disease.[16,17]

Despite appropriate use of analgesia and non-drug therapies, chemotherapy, radiotherapy and non-pharmacological treatments by multidisciplinary teams, a considerable number of patients will still have uncontrolled pain or unacceptable side effects, or both.

Such patients should be considered for some form of invasive analgesic technique. This may range from a simple nerve block to more invasive techniques such as regional or neurodestructive blocks.

The choice of technique is influenced by:

- Patients expectations.
- Prognosis and required duration of analgesia.
- Pathology.
- Availability of experts and trained staff.

A basic rule is that the technique with the least likelihood of severe side effects should be chosen. In general, neurodestructive techniques should be reserved for when other measures have failed or when life span is obviously limited (Table 3).

4.6. *Spinal routes of drug delivery*

With improvements in catheter and pump technology, use of spinal lines is becoming more common in pain control. If the technique is carried out by trained staff, complication rates are low, allowing flexible, long-term analgesia that can be used in an outpatient setting. Catheters can be inserted either into the epidural space or into the subarachnoid (intrathecal) space, where the cerebrospinal fluid is found. The line may be tunnelled subcutaneously to reduce risks of infection and movement of the catheter. The choice of technique depends on several factors as outlined in Table 3.

The main advantages of spinal delivery of drugs are:

1. A marked reduction in opioid dose required and therefore fewer side-effects.
2. The use of drugs such as lignocaine which can control incident pain very effectively.

In addition, drugs such as clonidine, midazolam and ketamine can be used via a spinal catheter. If small volume infusions are used, e.g. 10-20 mls over 24 hours via a pump device, this usually avoids any major or sensory side-effects and patients can retain bowel and bladder control along with mobility.[7]

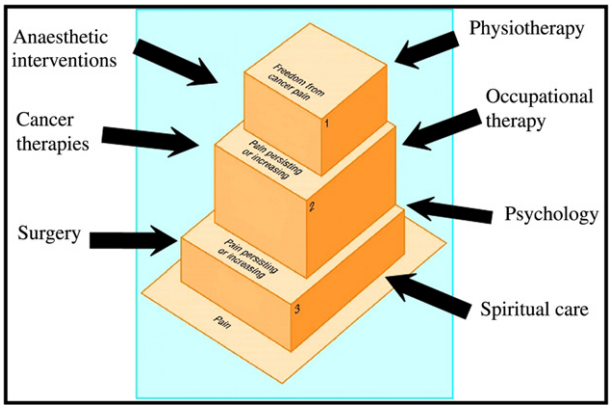

Fig. 3 – Integration of other interventions to the WHO ladder.

5. Conclusion

Treatment of cancer pain is integral to the successful management of the cancer patient. The principles of the WHO analgesic ladder should be followed and integrated with other aspects of care. Neuropathic pain can be a clinical challenge. Early involvement of an anaesthetic colleague with an interest in cancer pain is critical in cases where pain is not controlled despite best efforts. Uncontrolled neuropathic pain is associated with marked changes in the central nervous system (central wind-up) which can confer opioid resistance. Patients with central wind-up are more likely to need complicated pharmacology or interventional analgesia. At all points, management of general distress will have a positive effect on pain control through a direct influence on pain pathways (See Fig. 3).

Conflict of interest statement

Professor Fallon and Dr Colvin have received educational grants from Pfizer and Archimedes.

Acknowledgements

Dr. Laird is supported by grants from the National Cancer Research Institute (SuPaC Fellowship), and the Beatson Oncology Centre, Glasgow, United Kingdom.

REFERENCES

1. Caraceni APR. An international survey of cancer pain characteristics and syndromes. *Pain* 1999;**82**:263–74.
2. Merskey H, Bogduk N. *Classification of Chronic Pain*. Second ed. Seattle: IASP Press; 1994.
3. Walker VA, Hoskin PJ, Hanks GW, White ID. Evaluation of WHO analgesic guidelines for cancer pain in a hospital-based palliative care unit. *J Pain Symptom Manage* 1988;**3**(3): 145–9.
4. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer* 1987;**59**(4):850–6.
5. Fallon M, Hanks G, Cherny N. Principles of control of cancer pain. *BMJ* 2006;**332**(7548):1022–4.
6. Mercadante S, Fulfaro F, Casuccio A, Barresi L. Investigation of an opioid response categorization in advanced cancer patients. *J Pain Symptom Manage* 1999;**18**(5):347–52.
7. Colvin L, Forbes K, Fallon M. Difficult pain. *BMJ* 2006;**332**(7549):1081–3.
8. Fallon MT, Hanks GW. Opioid-resistant pain: sense or nonsense? *The Pain Clinic* 1993;**6**:205–6.
9. Grond S ZD, Diefenbach C, Radburch L, Lehman KA. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain* 1996;**64**:107–14.
10. Glover J, Dibble SL, Dodd MJ, Miaskowski C. Mood states of oncology outpatients: does pain make a difference? *Journal of Pain & Symptom Management* 1995;**10**(2):120–8.
11. Lloyd-Williams M, Dennis M, Taylor F. A prospective study to determine the association between physical symptoms and depression in patients with advanced cancer. *Palliat Med* 2004;**18**(6):558–63.
12. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;**118**(3):289–305.
13. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev 2007(4):CD005454.
14. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage* 2000;**20**(4):246–52.
15. Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. *Pain* 2002;**97**(3):275–81.
16. Mercadante S, Catala E, Arcuri E, Casuccio A. Celiac plexus block for pancreatic cancer pain: factors influencing pain, symptoms and quality of life. *J Pain Symptom Manage* 2003;**26**(6):1140–7.
17. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002;**20**(19):4040–9.