Symposium VI

Total Care in Cancer Pain Management

Advances in cancer pain management

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35th April, 2010

Total Care in Cancer Pain

Pain Assessment

Pain Management
Total Pain Concept

- **PHYSICAL**
  - Depression
  - Anxiety
  - Angry
  - Isolation

- **PSYCHO-LOGICAL**
  - Multidisciplinary team approach

- **SOCIAL**
  - QOL
    - Social activity
    - With friends & families

- **SPIRITUAL**
  - Multidisciplinary team approach

Total Cancer Pain

**Meaning of cancer pain**
- Close to death
- Death anxiety
- Relation with God
- Life review - punishment

**Somatic therapies**

**Advances in cancer pain management**
Morphine and alternative opioids in cancer pain: the EAPC recommendations

Expert Working Group of the Research Network of the European Association for Palliative Care

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Summary: An expert working group of the European Association for Palliative Care has revised and updated its guidelines on the use of morphine in the management of cancer pain. The revised recommendations presented here give guidance on the use of morphine and the alternative strong opioid analgesics which have been introduced in many parts of the world in recent years. Practical strategies for dealing with difficult situations are described presenting a consensus view where supporting evidence is lacking. The strength of the evidence on which each recommendation is based is indicated. © 2001 Cancer Research Campaign http://www.bjocancer.com

Keywords: morphine; alternative opioids; European guidelines
**EAPC Guidelines: Summary Points**

1. Morphine is the first choice of strong opioid for moderate to severe pain  
   Evidence Grade C

2. Methadone is an effective alternative but it have pronounced inter-individual differences in its plasma half life (17-100hrs), relative analgesic potency and duration of action  
   Evidence Grade C

3. Transdermal fentanyl is an effective alternative but is best reserved for patients whose opioid requirement are stable  
   Evidence Grade B

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A substantial minority of patients treated with morphine (10-30%) do not have successful outcome because of:

1. Intolerable adverse effect – CNS, GI
2. Inadequate analgesic even rapid increase the dose of opioids
3. Combination of both

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**Opioid Switching**

become one of the common practice in Palliative Care
What is Opioid Switching?

Is defined as the practice of converting a patient from one opioid to another, aimed at finding the most favorable balance between analgesic and side effects.

Cochrane review on opioid switching to improve pain relief and drug tolerability

Quigley C. Cochrane Review 2009
52 reports identified, comprising 23 case reports, 15 retrospective studies, 14 prospective uncontrolled studies.

- Majority use morphine as first line opioid and most frequently used second-line opioid was methadone
- All reports apart from one, concluded that opioid switching is a useful clinical manoeuvre for improving pain control and reduce opioid-related side effects

Conclusion:

- For patients with inadequate pain relief and intolerable opioid-related toxicity, a switch to an alternative opioid may be the only option for symptomatic relief
- However evidence to support the practice of opioid switching is largely anecdotal or based on observational and uncontrolled studies
- Randomised trial including studies where a patient acts as their own control are needed to
  1. Establish the true effectiveness of this practice
  2. To determine which opioid should be used as first line or second line
  3. To standardise conversion ratio
Morphine-Methadone Opioid Rotation in Cancer Patients: Analysis of Dose Ratio Predicting factor

MA Benitez-Rosario, et al
J Pain Symptom Management, 2009;37(6), 1061-1068

Evaluate potential predictive factors of Morphine-Methadone dose ratio (MMEDR) in a cohort of cancer patients who underwent opioid switching because of uncontrolled pain and/or morphine side effects
**MMEDR predicted from Multivariate Linear Regression Analysis**

<table>
<thead>
<tr>
<th>Reason for rotation</th>
<th>Previous oral morphine dosage</th>
<th>MMEDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side effects of Morphine</td>
<td>&gt;300mg/day</td>
<td>9.1:1</td>
</tr>
<tr>
<td>Pain</td>
<td>&gt;300mg/day</td>
<td>4.9:1</td>
</tr>
<tr>
<td>Side effects of Morphine</td>
<td>&lt;300mg/day</td>
<td>5.6:1</td>
</tr>
<tr>
<td>Pain</td>
<td>&lt;300mg/day</td>
<td>3:1</td>
</tr>
</tbody>
</table>

**Postulated mechanism**

- Incomplete cross tolerance with previous opioids, which make methadone more potent than anticipated
- Hyperalgesic state induced by previous chronic opioid (morphine) used
- NMDA antagonist characteristics of methadone make methadone more potent when doing switching
Breakthrough Pain

Neuropathic Pain

- Abrupt, short lived and intense pain that “breaks through” the around the clock analgesia that control persistent pain.

**IDEAL MEDICATIONS:**
- Rapid onset, short acting, easy administered
A review on the use of opioids for management of breakthrough pain in cancer patients included:

- 4 randomised control studies with 393 participants,
- all studied the efficacy of transmucosal fentanyl citrate (OTFC) compared to placebo and morphine.

Cochrane database of systemic review, 2005

**Oral Transmucosal Fentanyl Citrate (OTFC)**

- OTFC consists of a fentanyl impregnated sweetened and hardened lozenge on a plastic handle and designed for breakthrough pain.
- Rapid onset 5-15 min, short duration of action of around 2 hrs.
- 6 doses available 200, 400, 600, 800, 1200 and 1600mcg available.
Results

- OTFC was superior to (1) placebo, (2) normal release morphine, (3) previous rescue medication in providing breakthrough pain relief at 15min and 30min.
- Successful dose of OTFC is determined by titration
- Mean dosage of successful OTFC varies from 587mcg to 811mcg (± 335 to 468mcg)
- No relationship between the successful dose of OTFC and the total daily around the clock opioid

Cochrane database of systemic review, 2005

New preparation – Fentanyl Buccal Soluble Film (FBSF)

- Fentanyl Buccal Soluble Film (Onsolis)
- FDA approved product for breakthrough cancer pain in 2009
- 5 doses strength available - 200mcg, 400mcg, 600mcg, 800mcg and 1200mcg
- Place the FBSF inside the cheek, it will dissolve within 15-30min
- Rapid onset – within 3min
- Duration of action – 2 hr
Neuropathic pain in cancer patient

Systemic review on pharmacological treatment on neuropathic pain

Search for studies on neuropathic pain related to cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proposed mechanism of action</th>
</tr>
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<tbody>
<tr>
<td>Anti-depressant</td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>Inhibition of serotonin &amp; norepinephrine reuptake</td>
</tr>
<tr>
<td>SNRI</td>
<td></td>
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<tr>
<td>Opioid</td>
<td></td>
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<tr>
<td>Opioid</td>
<td>Modulates the perception of pain via opioid receptor</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Acts through both u opioid receptor &amp; inhibit uptake of norepinephrine</td>
</tr>
<tr>
<td>Anti-convulsant</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Modulation of high voltage activated Ca channels</td>
</tr>
<tr>
<td>Valproate, lamotrigine,</td>
<td>Blockade of voltage-gated sodium channels</td>
</tr>
<tr>
<td>carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Gabapentin, pregabalin</td>
<td>Modulates voltage-gated Ca channels via binding to $\alpha_2$ $\delta$ subunit of presynaptic</td>
</tr>
<tr>
<td>NMDA antagonist</td>
<td>neurons</td>
</tr>
<tr>
<td>Ketamine, dextromethorphan, memantine, and amantadine</td>
<td>NMDA antagonist</td>
</tr>
<tr>
<td>Topical anesthetic</td>
<td></td>
</tr>
<tr>
<td>Lidocaine patch</td>
<td>Acts by blocking sodium channels thereby reducing ectopic nerve impulses</td>
</tr>
</tbody>
</table>
Only few clinical trials have specifically evaluated the use of antidepressant and anticonvulsant for cancer pain, results are controversial.

Kalso E, et al. Pain, 1996
Mercadante S, et al. Tumori 2002
Tasmuth T. et al, Pain 2002
Reuben SS et al. Journal of Pain and Symptom management 2004
Cochrane Database of systematic Reviews, 2005
Neuropathic Pain:

Is Methadone superior to Morphine?

- Methadone also has NMDA receptor activity as an antagonist
- No trial evidence to support the postulation that methadone has a particular role in neuropathic pain of malignant origin

_Cochrane Database of systematic Reviews, 2008_

Ketamine – Cancer Pain

- Only limited studies on use of ketamine in subanesthetic dose for neuropathic pain in cancer patients, most of studies were case reports
- Latest Cochrane Review 2009 identified only 4 RCTs. Only two were included (Yang 1996, Mercadante 2000)
10 Patients with KPS 50 or above
• Pain not controlled by morphine. No adjuvant drugs.
• In slow iv bolus over 30 min: Ketamine 0.25mg/kg or 0.5mg/kg or saline
  – Each subject will receive all the three treatments in randomized order
  – Given on 3 separate days, at least 2 days apart
• Evaluated at T0, T30, T60, T120, T180 for pain and side effects

Results: Pain intensity significantly decrease since T30 till T 180
More effective at higher dose, but more drowsiness in higher dose

“Burst” Ketamine for Refractory Cancer Pain: An Open-Label Audit of 39 Patients

• Prospective, multicenter, unblinded
• Pain not controlled by opioid with adjuvants
• Pain score >3 on a 0-10 VRS
• Burst ketamine infusion for 3 to 5 days in doses of 100mg to 500mg

Results:
67% had 50% decrease in pain intensity or reduction in opioid dose
After cessation of ketamine 70% maintain good control up to 8 weeks
12 reported psychomimetic S/E like hallucinations, drowsiness and dizziness
Current evidence is insufficient to assess the benefits and harms of ketamine in neuropathic pain management due to limited randomized control trials,

Cochrane Database of systematic Reviews, 2009

Use of bisphosphonates in cancer related bone pain
Generation of bisphosphonates

1. Clodronate – oral (limited by GI side effect), iv
2. Pamidronate – iv doses range from 60-90mg over 2hrs every 3-4 weeks
3. Zoledronic acid – iv doses 4-8mg over 15 min every 3-4 weeks
4. Ibandronate (New generation) – oral 50mg daily, iv 6mg over 1hr every 3-4 weeks

Focus on:
- Evidence of use of zoledronic acid and Ibandronate on prevention of skeletal-related events and bone pain

Efficacy of zoledronic acid in patients with various tumor types
Jean-Jacques Body, Support Care Cancer, 2006

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Breast cancer and multiple myeloma (25 months)</th>
<th>Hormonal-refractory prostate cancer (24 months)</th>
<th>Lung and other solid tumors (9 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zoledronic acid, 4mg (n=561)</td>
<td>Palmidronate, 90mg (n=555)</td>
<td>Zoledronic acid, 4mg (n=214)</td>
</tr>
<tr>
<td>Primary Patients with &gt;/=1 SRE (%)</td>
<td>47</td>
<td>51</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>p=0.028</td>
<td>P=0.127</td>
<td></td>
</tr>
<tr>
<td>Secondary Time to first SRE (days)</td>
<td>376</td>
<td>356</td>
<td>488</td>
</tr>
<tr>
<td></td>
<td>P=0.151</td>
<td>P=0.009</td>
<td>P=0.023</td>
</tr>
<tr>
<td>Skeletal morbidity rate (SMR)</td>
<td>1.04</td>
<td>1.39</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>P=0.084</td>
<td>P=0.006</td>
<td>P=0.017</td>
</tr>
</tbody>
</table>

SRE: Pathological fracture, spinal cord compression, RT to bone and surgery to bone
SMR: Mean annual incidence of skeletal related events
Zoledronic acid: Prevention of SRE

• Zoledronic acid 4mg iv shown evidence of effectiveness of SRE reductions in breast cancer, multiple myeloma, prostate cancer, lung and other solid tumor.

• Whereas previous generation of bisphosphonate (clodronate and palmidronate) only shown efficacy in breast cancer and multiple myeloma

Jean-Jacques Body, Support Care Cancer, 2006

Zoledronic acid: Effect on bone pain

• In patient with breast cancer and bone metastasis, significant difference in pain score treated with zoledronic acid Vs placebo (p=0.0004)

• In patient with bone pain due to other primary, zoledronic acid had NO significant effect

Jean-Jacques Body, Support Care Cancer, 2006
Ibandronate: Prevention of SRE

- Iv Ibandronate (6mg over 1-2 hr) and oral ibandronate (50mg qd), significantly ↓skeletal morbidity period (p=0.004) and risk of SRE (40% and 38%, p = 0.003 and p< 0.001 respectively) in patients with breast cancer and bone metastasis


Ibandronate: Prevention of SRE

- A trial included 73 patients with colorectal cancer metastasis to bone:
  - treated with iv ibandronate 6mg
  - significant lower proportion of patient with SRE
  - (39 Vs 78% for placebo, p =0.019)

Heres P et al. EUR J Cancer Care, 2007
Ibandronate:
Effect on bone pain

• Both iv and oral ibandronate shown significant reduction in bone pain score compared with placebo (p < 0.001) in breast cancer with bone metastasis


High dose Ibandronate:
Effect on bone pain

• Open labelled trial of 18 patients with opioid-resistant bone pain due to various primary tumor:
  – 4mg iv ibandronate x 4 consecutive days,
  – leading to significant reduction in bone pain scores within 7 days (p< 0.001)
  – Pain reduction effect sustained for 6 weeks

A review included 30 randomised controlled studies of 3682 patients with bone metastasis from different primary tumors:

- evidence to support effectiveness of bisphosphonate in providing some pain relief for bone metastasis but insufficient evidence for immediate effect or as first line therapy
- It should only be considered when other analgesic and RT are inadequate for pain control

_Cochrane Database of systematic Reviews, 2008_

**What are cannabinoids and how do they function?**

- Cannabis contains 60 or more cannabinoids (CBs)
- Two active components shown evidence in relieving cancer related pain
  - Delta-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
- Act through specific CB receptors:
  - CB1 : distributed in CNS
  - CB2 : associated with cells and tissues related to immune system
Pharmacological effects of THC and CBD

<table>
<thead>
<tr>
<th>Pharmacological effect of THC</th>
<th>Pharmacological effects of CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Muscle relaxation</td>
<td>? through anti-inflammatory and</td>
</tr>
<tr>
<td>Antiemesis</td>
<td>immunomodulatory effect</td>
</tr>
<tr>
<td>Appetite stimulant</td>
<td>Muscle relaxation</td>
</tr>
<tr>
<td>Psychoactivity</td>
<td>Neuroprotective effects</td>
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<tr>
<td></td>
<td>Anticonvulsant</td>
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<tr>
<td></td>
<td>Anxiolytic effects</td>
</tr>
<tr>
<td></td>
<td>Reduce psychoactive effects of</td>
</tr>
<tr>
<td></td>
<td>THC</td>
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</tbody>
</table>

**Journal of pain and Symptom Management, 2010**

Original Article

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

- Multicenter, double-blind, randomized, placebo controlled trial
- Total 177 patients with cancer pain,
- who experienced inadequate analgesia (NRS >4)
- despite chronic opioid dosing,
- random assigned to 3 groups (THC: CBD, THC extract, placebo)
- self titrate to optimal dose dose during 1st week
<table>
<thead>
<tr>
<th></th>
<th>THC:CBD extract (Sativex) N= 60</th>
<th>THC extract N= 58</th>
<th>Placebo (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline mean pain NRS</td>
<td>-1.37 P=0.014</td>
<td>-1.01 P=0.245</td>
<td>-0.69</td>
</tr>
<tr>
<td>% of patients had &gt; 30% pain reduction in intensity</td>
<td>43% P=0.006</td>
<td>23% P=0.28</td>
<td>21%</td>
</tr>
<tr>
<td>Median dose of background opioid medications</td>
<td>79% no change</td>
<td>77% no change</td>
<td>80% no change</td>
</tr>
<tr>
<td>Change from baseline the number of breakthrough opioid</td>
<td>56% no change</td>
<td>56% no change</td>
<td>63% no change</td>
</tr>
<tr>
<td>Adverse effect</td>
<td>Mild to moderate somnolence, dizziness and confusion, similar in all 3 groups</td>
<td></td>
<td></td>
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</tbody>
</table>

**Conclusion**

- This study concluded the THC: CBD extract is a useful adjunctive treatment for relief cancer pain
- However the role of CBD in cannabis preparation is still unclear
- Further studies are warranted
What is Sativex (THC:CBD)

• Sativex is an oromucosal spray
• 1 spray contain 2.7mg THC and 2.5mg CBD
• Approved in Canada for adjunctive analgesic treatment in patient with advanced cancer pain despite highest tolerated strong opioid in 2007
• Not approved by FDA

No matter how advance in pharmacology

The key for good cancer pain control, should include detail Pain Assessment
Total Pain Concept

- **Somatic therapies**
- **Multidisciplinary Team approach**

**PHYSICAL**
- Depression
- Anxiety
- Depression
- Multidisciplinary Team approach

**PSYCHOLOGICAL**
- Loss of appetite
- Fatigue
- Insomnia

**SOCIAL**
- Social activity with friends & families

**SPIRITUAL**
- Meaning of cancer pain
- Life review - punishment

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**The End**
Methadone Versus Morphine as a first-line strong opioid for cancer pain: A randomized, double-blind Study

Bruera E, et al. Journal of Clinical Oncology, 2004

A total of 103 cancer patients were randomly assigned to methadone group and morphine group

<table>
<thead>
<tr>
<th>Methadone group</th>
<th>Morphine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 patients</td>
<td>54 patients</td>
</tr>
<tr>
<td>Methadone 7.5mg bd orally</td>
<td>SR morphine 15mg bd orally</td>
</tr>
<tr>
<td>Methadone 5mg q4h prn</td>
<td>Immediate release morphine 5mg q4h prn</td>
</tr>
<tr>
<td>70% reported more than 20% improvement in pain at 4 weeks</td>
<td>70% reported more than 20% improvement in pain at 4 weeks</td>
</tr>
<tr>
<td>22% opioid-related drop outs</td>
<td>6% opioid-related drop outs (p=0.019)</td>
</tr>
</tbody>
</table>
Methadone did not produce superior analgesic efficiency or overall tolerability at 4 weeks compared with morphine as a first line strong opioid for cancer pain.

**Conversion ratio**

**morphine → Methadone**

- A dose ratio when switching from morphine to methadone varies widely in different studies from 16:1 to 2.5:1
- Conversion regime:
  - Fixed dose ratio
  - Ad Libitum

<table>
<thead>
<tr>
<th>Total daily oral dose of morphine (EDDM) before conversion</th>
<th>Morphine: Methadone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 90mg</td>
<td>4:1</td>
</tr>
<tr>
<td>90 - 300mg</td>
<td>8:1</td>
</tr>
<tr>
<td>&gt; 300mg</td>
<td>12:1</td>
</tr>
</tbody>
</table>


Ad Libitum


- A fixed dose of methadone, 1/12 of total daily oral dose of morphine (EDDM), up to 30mg per dose of methadone was given to patient Q3h PRN when patient rated pain as moderate or above in severity

- Ad libitum prescription continues until the demand for methadone reduce or stabilise

- Calculate total daily dose of methadone and then divided to be given bd or tds

- If pain not controlled after 1 week on regular bd/ tds dose of methadone, methadone increased by 50% according to the same time schedule

Rationale: high variable pharmacokinetics, difficult to have fixed ratio

Gabapentin – Cancer Pain

- Gabapentin also demonstrated to have beneficial analgesic effect in neuropathic pain specifically related to cancer

- A multicentre, randomized, double-blind, placebo controlled trial included 121 patients with neuropathic pain due to cancer found significant difference of pain intensity between gabapentin (600-1800mg/d) and placebo group, p = 0.025.

Zoledronic acid: Effect on Renal function

• Adverse Event Reporting System of US FDA: 72 cases of renal dysfunction associated with zoledronic acid were identified from Aug 01 to March 03
• Of 72 patients, 27 required dialysis and 18 died


Warning of nephrotoxicity and restrictions for patient with varying degrees of renal impairment was updated in product label

Ibandronate: Effect on renal function

• Results from clinical studies demonstrated that ibandronate has a renal safety profile comparable with placebo
• No dosage adjustment is required in mild to moderate renal impairment
• Renal function monitoring is not mandatory at physician’s direction
Summary

• Strong evidence suggested the use of bisphosphonate on prevention of skeletal complication in multiple myeloma and breast cancer with bone metastasis

• No consensus on its use in other tumor

• Bisphosphonate can be used for pain relief in bone metastasis but it should be considered as adjunct to other analgesic or RT

Summary

• Zoledronic acid is the first bisphosphonate demonstrated to have beneficial effect in reduction of SRE in patient with bone metastasis from lung and other solid tumor other than breast cancer and multiple myeloma

• Ibandronate is available in both iv and oral form which shown beneficial effect in reduction of SRE and pain score in breast cancer with bone secondary.

• Use of intense and high dose of ibandronate in severe and refractory bone pain need further investigation