Management of pain in head and neck cancer

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2009

Possible conflict of interest disclosure

I currently have, or I have had in the past two years, an affiliation with/or financial interests in a business corporation, or I receive remuneration, royalties, or research grants from a business corporation

2006-2009: Advisory board Johnson & Johnson
2008: Advisory board Merck
2009: Advisory board Nycomed

Epidemiology
Management of cancer pain in head and neck cancer: prevalence

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Pain(%) (95%CI)</th>
<th>N Reports</th>
<th>N Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/neck</td>
<td>70 (51-88)</td>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>59 (44-74)</td>
<td>9</td>
<td>564</td>
</tr>
<tr>
<td>Lung/bronchus</td>
<td>55 (44-67)</td>
<td>7</td>
<td>1546</td>
</tr>
<tr>
<td>Breast</td>
<td>54 (44-64)</td>
<td>7</td>
<td>420</td>
</tr>
<tr>
<td>Uro-genital</td>
<td>52 (40-60)</td>
<td>4</td>
<td>336</td>
</tr>
<tr>
<td>Gynecological</td>
<td>60 (50-71)</td>
<td>6</td>
<td>372</td>
</tr>
</tbody>
</table>

van den Beuken-van Everdingen MH et al. Ann Oncol 2007

Management of cancer pain in head and neck cancer: prevalence

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Status</th>
<th>Pain(%)</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Foley (87)</td>
<td>At diagnosis</td>
<td>80</td>
<td>Tumor-related</td>
</tr>
<tr>
<td>Grond (93)</td>
<td>At diagnosis</td>
<td>83</td>
<td>Tumor-related</td>
</tr>
<tr>
<td>Agarwal (08)</td>
<td>At diagnosis</td>
<td>28</td>
<td>Treatment-related</td>
</tr>
<tr>
<td>Logan (08)</td>
<td>5-year survivors</td>
<td>99</td>
<td>Advanced head and neck cancer</td>
</tr>
<tr>
<td>Karvonen (08)</td>
<td>Within 2 years after diagnosis</td>
<td>43</td>
<td>Metallic taste predicts pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain score was significantly associated with survival</td>
</tr>
</tbody>
</table>

Causes and types
Management of cancer pain in head and neck cancer: causes

- Tumor
  - Bone invasion or metastatic disease
  - Compression of spinal cord/other structures
  - Neural compression, neural damage
  - Obstruction glandular structures
  - (Para-neoplastic syndromes)
- Cancer treatment
  - Surgery (resection, reconstruction, acute and late side effects)
  - Chemotherapy (acute and late side effects e.g. stomatitis, neuropathy, inflammation)
  - Radiotherapy (acute and late side effects e.g. mucositis, neuropathy, inflammation)
- Non-cancer related pain
- Pain of unknown origin

Management of cancer pain in head and neck cancer: types

- Temporal relationship
  - Acute pain
  - Chronic pain
  - Incident pain/break through pain
- Physiopathological mechanism
  - Nociceptive pain
    - Somatic pain
      - Deep
      - Superficial
    - Visceral pain
  - Neuropathic pain

Management of cancer pain in head and neck cancer: multi-dimensional process

- Physical aspects
  - Cancer pain
  - Other somatic symptoms (e.g. cough, nausea, dysphagia)
- Psychological aspects
  - Frustrations, depression, anxiety
- Social aspects
  - Financial, place in family, job loss
- Spiritual aspect
  - Meaning of disease, life

  Multidisciplinary team approach
Management of cancer pain in head and neck cancer: nociceptive pain

- Nociceptive pain
  - Transduction
  - Transmission
  - Perception

Management of cancer pain in head and neck cancer: nociceptive pain

1. Secretion various agents
   1. Prostaglandins
   2. Cytokines
   3. RANK ligand
   4. Growth factors
2. Inflammation recruitment of inflammatory cells
   1. Prostaglandins
   2. Cytokines
   3. Reduced pH
   4. Activation of osteoclasts with bone destruction
   5. Sequestration osteoblast-derived osteoprotegerin
   6. Invasion of adjacent structures

(Interleukin, PG = prostaglandin, ET-1 = endothelin-1, RANK = receptor activator for nuclear factor-B, COX-2 = cyclo-oxygenase 2, TNF = tumor necrosis factor)


Management of cancer pain in head and neck cancer: nociceptive pain-receptors

Management of cancer pain in head and neck cancer: nociceptive pain-inflammation
Management of cancer pain in head and neck cancer: nociceptive pain-transmission

- Interference with pain transduction
  - Redrawal of traumatic factors
  - Interference with mediators

Management of cancer pain in head and neck cancer: nociceptive pain-perception

- Interference with pain transduction
  - Redrawal of traumatic factors
  - Interference with mediators

Management of cancer pain in head and neck cancer: nociceptive pain-modulation

- Interference with pain transduction
  - Redrawal of traumatic factors
  - Interference with mediators
- Interference with pain transmission
- Interference with pain perception
Management of cancer pain in head and neck cancer: nociceptive pain-modulation

<table>
<thead>
<tr>
<th>Ligand</th>
<th>System</th>
<th>Receptor</th>
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<tbody>
<tr>
<td>Dynorphin</td>
<td>Intraspinal</td>
<td>K-opioid receptor</td>
</tr>
<tr>
<td>Enkephalin</td>
<td>Intraspinal</td>
<td>μ- and δ-opioid receptor</td>
</tr>
<tr>
<td>Endorphin</td>
<td>Midbrain</td>
<td>μ-opioid receptor</td>
</tr>
<tr>
<td>Orphanin</td>
<td>Midbrain</td>
<td>δ-opioid receptor</td>
</tr>
<tr>
<td>GABA</td>
<td>Intraspinal</td>
<td>GABA receptors</td>
</tr>
<tr>
<td>Glycine</td>
<td>Intraspinal</td>
<td>Glycine receptors</td>
</tr>
<tr>
<td>Anandamide</td>
<td>Intraspinal</td>
<td>CB1 receptors</td>
</tr>
<tr>
<td>5-hydroxytryptamine (HT)</td>
<td>Bulbospinal</td>
<td>5-HT3 receptor</td>
</tr>
<tr>
<td>Nor-epinephrine</td>
<td>Bulbospinal</td>
<td>α2 receptors</td>
</tr>
</tbody>
</table>

Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

Reference:
Taylor et al. J Pharmacol Exp Ther 2001

Reference:
Taylor et al. J Pharmacol Exp Ther 2001
Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

Kumar et al. Cochrane Database Syst Rev 2006

Klepstad P et al. Tidsskr Nor Laegeforen 2005
Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

<table>
<thead>
<tr>
<th></th>
<th>μ1</th>
<th>μ2</th>
<th>κ</th>
<th>δ</th>
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</thead>
<tbody>
<tr>
<td>Supraspinal analgesia</td>
<td>x</td>
<td>x</td>
<td></td>
<td>(x)</td>
</tr>
<tr>
<td>Spinal analgesia</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular depression</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothemia</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermia</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuresis</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Anti-diuresis</td>
<td>x</td>
<td>(x)</td>
<td>(x)</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>x</td>
<td>(x)</td>
<td>(x)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>x</td>
<td>(x)</td>
<td>(x)</td>
<td>x</td>
</tr>
<tr>
<td>Gastric emptying/acid secretion</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Euphoria</td>
<td>x</td>
<td></td>
<td></td>
<td>(x)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>x</td>
<td></td>
<td>(x)</td>
<td></td>
</tr>
<tr>
<td>Tolerance/dependency</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions/stress/shock</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Neuropathic pain
Management of cancer pain in head and neck cancer: neuropathic pain

A. Transcription and axonal trafficking of sodium channels to the site of injury and concomitant attenuation of potassium channels hyperexcitable and ectopic activity
B. At the cell body of primary afferent neurons sympathetic neuronal sprouting
C. Changes in gene transcription and activation of various kinases and proteins. Following activation, microglia release various pro-nociceptive cytokines (IL-1, TNF, neurotrophins)

Gilron I. et al. CMAJ 2006

Evaluation of pain

Management of cancer pain in head and neck cancer: evaluation

- Anamnesis
- Pain evaluation scales
  - Numerical
  - VAS
- Clinical examination
- Imaging
Management of cancer pain in head and neck cancer: evaluation

- Pain evaluation instruments
  - Neuropathic pain (DN4) questionnaire

Treatment

Etiologic treatment
Management of cancer pain in head and neck cancer: anti-cancer treatment

- **Anti-cancer treatment**
  - Surgery: lack of data of effect on pain control
  - Radiotherapy: data of beneficial effect in bone metastases
  - Chemotherapy: lack of data of effect on pain control

- **Prevent and treat side effects of treatment**
  - Treatment-induced mucositis
    - Radiotherapy: 85% (Grade 3–4: 59%)  
    - Chemo-radiation: 98% (Grade 3–4: 75%)  
    - Chemotherapy: 40%


Management of cancer pain in head and neck cancer: treatment-induced mucositis


Management of cancer pain in head and neck cancer: treatment-induced mucositis

Management of cancer pain in head and neck cancer: treatment-induced mucositis

Several of the interventions have some benefit at preventing or reducing the severity of treatment-related mucositis

- The strength of the evidence is variable
- There is a need for well designed and conducted trials with sufficient numbers of participants

Symptomatic treatment
Management of cancer pain in head and neck cancer: fundamental treatment principles

- According to the pain characteristics

<table>
<thead>
<tr>
<th>neuropathic pain</th>
<th>nociceptive pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>spontaneous pain</td>
<td>evoked pain</td>
</tr>
<tr>
<td>dysesthesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>paresthesia</td>
<td>hyperalgesia</td>
</tr>
<tr>
<td>allodynia</td>
<td>hyperpathia</td>
</tr>
<tr>
<td>wind-up</td>
<td>sensory</td>
</tr>
</tbody>
</table>

Management of cancer pain in head and neck cancer: symptomatic treatment

- Medication
  - Analgesics
    - Adjuvant analgesics
  - Interventional techniques
    - Physiotherapy
    - Neurolytic/neurostimulatory interventions
    - Acupuncture
    - Other
- Psychological support
- Social support
- Spiritual support

Management of cancer pain in head and neck cancer: analgesics

- By the clock
  - Medication is given regularly
    - Appropriate medication for breakthrough pain
    - Readily access to medication
- By the easiest way
  - Medication is given by the mouth/transdermal
- By the ladder
  - Medication according to pain intensity
    - Medication potency sequentially escalated
- For the individual patient
  - Adapted to the organ function/co-morbidity/age
    - Careful and regular monitoring essential
    - Additional medication for side effects
Management of cancer pain in head and neck cancer: analgesics

- Pain ladder by the World Health Organization

  - **Step 1:** Non-opioids (e.g., paracetamol) or immediate-release opioids
  - **Step 2:** Weak opioids (e.g., codeine) with or without non-opioids
  - **Step 3:** Strong opioids (e.g., morphine) with or without non-opioids

**Paracetamol**
- Simplest and safest analgesic
- Mechanism of action not well understood
  - Central effect
  - COX inhibitor
- Indications
  - Nociceptive pain
  - (Chemotherapy-induced) Neuropathy
- Side effects
  - Sweating
  - Hepatotoxicity

Management of cancer pain in head and neck cancer: analgesics level I

**Non-steroidal anti-inflammatory drugs**
- Diverse groups
- Main mechanism of action = reduction PG synthesis
- Ceiling analgesic effect
- Opioid dose-sparing effect
- Indications
  - Bone pain
  - Inflammatory pain
- Side effects
  - Gastrointestinal side effects
  - Renal failure
  - Bleeding disorders
Management of cancer pain in head and neck cancer: analgesics level II-III

**Opioids**
- Mechanism of action
  - Interact with opioid receptors
  - Modulate pain transmission and pain perception
- Differ in
  - Receptor activation
  - Receptor affinity
  - Solubility
  - Body distribution
  - Metabolism
  - Administration
- Can be combined with level I medication

**Management of cancer pain in head and neck cancer: analgesics level II-III**

**Receptor activation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Opioid receptor activation</th>
<th>µ</th>
<th>κ</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>A(1+2)</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>A(1)</td>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>A</td>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>a</td>
<td></td>
<td></td>
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</tbody>
</table>

**Management of cancer pain in head and neck cancer: analgesics level II-III**

**Receptor affinity**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low</th>
<th>Affinity</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td>Morphine</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Management of cancer pain in head and neck cancer: analgesics level II-III

• Solubility

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Morphine</td>
<td>+</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>+</td>
</tr>
<tr>
<td>Fentanyl (L)</td>
<td>+</td>
</tr>
<tr>
<td>Methadone (L)</td>
<td>+</td>
</tr>
<tr>
<td>Hydromorphone (H)</td>
<td>+</td>
</tr>
</tbody>
</table>

Management of cancer pain in head and neck cancer: analgesics level II-III

• Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolisation</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>Morphine</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP2D6</td>
<td>Morphine</td>
</tr>
<tr>
<td>Morphine</td>
<td>UGT1A10</td>
<td>M3G</td>
</tr>
<tr>
<td>Hydrocodeine</td>
<td>UGT1A10</td>
<td>M3G</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CYP3A4</td>
<td>M3G</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP3A4</td>
<td>M3G</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP2D6 (poor/rapid)</td>
<td>M3G</td>
</tr>
</tbody>
</table>

Management of cancer pain in head and neck cancer: analgesics level II

• Codeine
  • Weak opioid activity

• Tramadol
  • Weak opioid activity
  • Noradrenaline + Serotonin uptake

• Tilidine
  • Weak opioid-like activity

• Buprenorphine
  • No ceiling effect for analgesia
  • Ceiling effects for side-effects
  • No restriction for future opioid use
  • Additive effect when co-administered with morphine
Management of cancer pain in head and neck cancer: analgesics level III

- Morphine
  - Still standard of care
- Hydromorphone
  - 5x potent as morphine
- Fentanyl
  - High potency (100x)
  - High lipid solubility
- Oxycodone
  - κ-opioid receptor
- Methadone
  - Racemic mix
  - NMDA-antagonist
  - μ-receptor agonist
  - Half-life: up to 190 hours
  - Steady state: 6 - 12 hours of analgesia

Management of cancer pain in head and neck cancer: analgesics II-III

- Side effects opioids
  - General: physical dependence, tolerance, hyperalgesia, itching
  - Gastrointestinal: delayed gastric emptying, nausea, vomiting, constipation
  - Neurological: sedation, dizziness, confusion, respiratory depression, muscle rigidity, myoclonus
  - Immunologic and hormonal dysfunction

Management of cancer pain in head and neck cancer: adjuvant analgesics for neuropathic pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing schedule</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical lidocaine</td>
<td>5% patch q 12 h</td>
<td>Erythema, rash</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>10-25 mg q 8h</td>
<td>Conduction disturbances, orthostatic hypotension, sedation, confusion, urinary retention, dry mouth, constipation</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60 mg q 12-24h</td>
<td>Sedation, ataxia, nausea, dry mouth, constipation, hypertension, anorexia</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg q 24h</td>
<td>Hypertension, ataxia, sedation, insomnia, nausea, hyperhidrosis, dry mouth, constipation, anxiety, anorexia</td>
</tr>
</tbody>
</table>

mg: milligrams; q: every Gilron I et al. CMAJ 2006
### Management of cancer pain in head and neck cancer: adjuvant analgesics for neuropathic pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing schedule</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100-200 mg/d</td>
<td>Sedation, ataxia, rash, diplopia, hyponatremia, agranulocytosis, nausea, diarrhea, hepatotoxicity, aplastic anemia</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300-600 mg/d</td>
<td>Sedation, ataxia, edema, weight gain, diplopia, nystagmus</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>50-150 mg/d</td>
<td>Sedation, ataxia, edema, diplopia, weight gain, dry mouth</td>
</tr>
</tbody>
</table>

mg: milligram; d: day

Gilron I et al. CMAJ 2006

### Management of cancer pain in head and neck cancer: adjuvant analgesics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Oral dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptics</td>
<td>Nausea, delirium, psychosis, agitation</td>
<td>2.5 mg q 8h</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Anxiety, muscle spasm, myoclonus, dystonia, delirium</td>
<td>2-10 mg q 6-8h</td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Pruritus, nausea</td>
<td>25-50 mg q 4-6h</td>
</tr>
<tr>
<td>Anti-histamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychostimulants</td>
<td>Somnolence</td>
<td>5-15 mg q 8-12h</td>
</tr>
</tbody>
</table>

Kg: kilogram; mg: milligram; q: every; h: hours; SC: subcutaneously

### Management of cancer pain in head and neck cancer: multi-combination treatment

- **Pain treatment**
  - According to pathogenesis
    - Nociceptive
      - Superficial somatic
      - Deep somatic
    - Visceral
    - Pure neuropathic
    - Mixed
  - Dominant mechanism of pain rather than intensity to determine sequence of analgesic therapy
Management of cancer pain in head and neck cancer: mechanism-based treatment strategy

- Tumor insult
- Dysfunction
- Pathological mechanisms
- Clinical symptoms

Disease State  Measurement  Clinical Syndrome

Based on the fact that various pathophysiologic types of pain have different sensitivities to distinct classes of analgesics.

Management of cancer pain in head and neck cancer: mechanism-based treatment strategy

- Neuroleptics (Tricyclic)
- Anti-depressants
- NMDA Receptor antagonists
- Anti-spasmodics
- Agonists
- Rational polypharmacy in multidisciplinary team approach to control pain

Management of cancer pain in head and neck cancer: conclusion

- Pain is prevalent in patients with head and neck cancer
- Pain evaluation is of crucial importance
- Pain treatment should be directed at
  - Causes
  - Symptoms
  - Pathophysiological mechanism
- Studies on pain in patients with head and neck cancer are needed