MANAGEMENT OF CANCER PAIN AND OTHER SYMPTOM CONTROL

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DISCLOSURE OF INTEREST

Nil to disclose!
OBJECTIVES

- Cancer pain
- Delirium
- Terminal agitation
- Recurrent ascites
CANCER PAIN
OBJECTIVES

- Incidence
- Assessment
- Pain management
- Management of opioid side effects
- Specific pain types
  - Bone pain
  - Neuropathic pain
- Interventional analgesia
- End of life
INCIDENCE

- Ranges:
  - 33% after curative treatment
  - 59% on anticancer treatment
  - 64% with advanced cancer

- Factors associated with development of chronic pain:
  - CIPN, radiation-induced brachial plexopathy, RT induced chronic pelvic pain and post surgical pain
  - Highest prevalence in pancreatic (44%) and H&N (40%)
  - Inadequately treated (solid and haematological cancers)
ASSESSMENT

• Assess and re-assess the pain and patient:
  - Causes, onset, type, site, radiating pain, duration, intensity, relief and temporal patterns, number of breakthrough pains,
  - Triggers/relieving factors
  - Effect of analgesics
  - Pain description
  - Physical examination
  - Investigations
  - Impact (patient and caregiver)
  - Alcohol/substance misuse
• Communication with patient and caregiver
If cognitive impairment, observe pain-related behaviours and discomfort to assess presence of pain (but not intensity)
PRINCIPLES OF PAIN MANAGEMENT

- Inform and involve patients
- ‘By the clock’ administration
- Oral route where possible
- Rescue medications for breakthrough pain
WORLD HEALTH ORGANISATION ANALGESIC LADDER (1986)

Renal impairment

Aspirin
Paracetamol
NSAID

Mild pain
Non-opioids +/- adjuvant

Mild – moderate pain
Weak opioids +/- non-opioid +/- adjuvant

Moderate - severe pain
Strong opioids +/- non-opioid +/- adjuvant

Give drugs:
By mouth
By clock
By ladder
For individual
Attention to detail

80% of pain controlled with this ladder

Morphine
Diamorphine
Oxycodone
Methadone
Alfentanil
Fentanyl
<table>
<thead>
<tr>
<th><strong>Routes of administration</strong></th>
<th>PO/SC/IV/IM/Rectal</th>
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<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>35% PO, ranging from 15–64%; 25% PR.</td>
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<tr>
<td><strong>Peak effect</strong></td>
<td>30–60min IM; 50–90min SC.</td>
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<tr>
<td><strong>Time to peak plasma concentration</strong></td>
<td>15–60min IR, PO 1–6h MR; 10–20min IM/SC;</td>
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<tr>
<td><strong>Half life</strong></td>
<td>1.5–4.5h PO; 1.5h IV.  (\text{Renal failure, M6G increases up to 7.5h})</td>
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<tr>
<td><strong>Duration of action</strong></td>
<td>3–6h IR; 12–24h MR</td>
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<tr>
<td><strong>Metabolism</strong></td>
<td>UGT2B7</td>
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<tr>
<td><strong>Metabolites</strong></td>
<td>M-6-G (10-15% Active) (\text{M-3-G (60-80% Inactive)})</td>
</tr>
<tr>
<td><strong>Receptor</strong></td>
<td>M-6-G acts on (\mu)-opioid receptor</td>
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OPIOIDS AND RENAL IMPAIRMENT

- Mod-severe renal impairment:
  - Use short acting preparations
  - Reduce dose and increase dose interval
  - Considerations for specific opioids, e.g. alfentanil
  - Individual considerations (analgesic need, prognosis, routes, formulations)
- Rules of thumb
  - Avoid codeine and dihydrocodeine
  - Both morphine and oxycodone have active metabolites which may accumulate
    - But inconsistency on the significance of any accumulation of oxycodone metabolites…..
  - Alfentanil, fentanyl and methadone metabolised in liver to inactive metabolites therefore safe!
ADVERSE EFFECTS OF OPIOIDS

- Common initial
  - Nausea & vomiting
  - Drowsiness
  - Unsteadiness
  - Delirium (confusion)

- Common ongoing
  - Constipation
  - Nausea & vomiting
  - Dry mouth

- Occasional
  - Sweating
  - Pruritus
  - Hallucinations
  - Myoclonus
  - Urinary retention

- Rare
  - Respiratory depression
  - Psychological dependence

Reduce dose
Opioid switch
Coanalgesic
Alternative approach (nerve block/RT)
Treatment of pain due to bone metastases

Zoledronic acid, denosumab or pamidronate (only in breast cancer) (plus calcium and vitamin D supplementation) should be given, in addition to analgesic therapy. These drugs showed to delay SREs and to reduce pain. Patients should undergo a preventive dental screening by dentistry prior to initiation the therapy with one of the drug. The optimal duration of these drugs is not completely defined.

USE ANALGESIC THERAPY

Uncomplicated bone metastases

Bone pain?

YES

Complicated bone metastases (spinal cord compression or impending fracture)?

YES

Radiotherapy and/or surgery should be promptly considered, when appropriate. Zoledronic acid, denosumab, or pamidronate should be given because showed to delay the first and subsequent SREs.

USE ANALGESIC THERAPY

NO

The same strategies suggested for uncomplicated bone metastases with or without bone pain

NO

Previous SRE: radiotherapy, bone surgery

YES

NO

Zoledronic acid, denosumab, or pamidronate should be given because showed to delay the first and the subsequent SREs.
BISPHOSPHONATES

- Indications (in cancer):
  - Tumour-induced hypercalcaemia
  - Prophylactically to reduce freq and severity of SRE (#, RT, surgery, SpCC, hypercalc) in patients with osteolytic lesions from MM, met breast and prostate
  - Bone pain (unlicensed)
- Cancer related increase in osteoclasts causes pain by:
  - Producing acid environment (stim sensory nerves)
  - Destroying sensory nerves
  - Causing mechanical instability

As adjuvant analgesic:
- Unlicensed
- Effect within 2 weeks
- Effect more likely in pt with breast cancer/myeloma and with IV
BISPHOSPHONATES: PHARMACOLOGY

- Pharmacology:
  - Regulators of bone metabolism
  - Taken up by osteoclasts and interfere with their function/induce cell death
  - Poorly absorbed PO & excreted unchanged via kidney
  - 2 classes:
    - Nitrogen containing (alendronate, ibandronic acid, pamidronate, zoledronic acid) inhibit pathway vital for normal cellular function
    - Non-nitrogen containing (clodronate, etidronate) form cytotoxic cytokines
    - Cellular effects extend to macrophages reducing production of cytokines → analgesic effect?
BISPHOSPHONATES: UNWANTED EFFECTS

- Systemic inflammatory reactions
  - Fever, myalgia, arthralgia, N&V (25-50% following IV within 48h); may be bone pain within 12h
  - Release of cytokines from infl cells?
  - Rx: paracetamol/NSAID prior to infusion

-Renal toxicity
- Osteonecrosis of jaw
  - Repeated low level trauma and ease of infection
  - Pain, trismus, discharge, exposed bone, sinusitis, numbness
  - Mean duration 1-2/3 years
  - Incidence unsure but could be around 10% zoledronic acid and 4% pamidronate
  - Risk factors: poor dental health, blood clotting disorders, anaemia, chemo, corticosteroids
  - Prevention key!

- Ocular inflammation
  - Typically within 2d
  - bilateral
DENOSUMAB

* Monoclonal antibody to RANKL (receptor activator of nuclear factor-kappa B) expressed on pre-osteoclasts (and T cells)
* Loss of osteoclasts from bone surface thereby decreasing bone resorption
* Unwanted effects:
  - Hypocalcaemia
  - Joint/muscle pain
  - Increased risk of infection
  - Hypersensitivity allergic reactions
  - Osteonecrosis jaw
  - Atypical femur fractures
* 120mg sc every 4 weeks (with calcium and Vit D suppl)
Assessment and treatment of neuropathic pain

**Semantic descriptor of neuropathic pain**

- **Allodynia**: pain caused by a stimulus which normally does not provoke pain.
- **Causalgia**: continuous burning pain, allodynia and hyperalgesia in succession or a traumatic nervous lesion; disturbed vasomotor functions are often intercurrent, as well as, later on, disturbances to trophism.
- **Central pain**: pain associated with a lesion of the central nervous system.
- **Dysesthesia**: unpleasant sensation of tingling, stabbing or burning whether spontaneous or provoked.
- **Hyperesthesia**: increase in sensitivity to specific stimuli.
- **Hyperalgesia**: increased response to a stimulus which is normally painful.
- **Hyperpathia**: painful syndrome characterised by increased reaction to a stimulus, especially a repetitive stimulus.
- **Paresthesia**: abnormal sensation, either spontaneous or evoked.

**Assessment tools**

- Neuropathic Pain scale
- Neuropathy Pain Symptom Inventory

**Assessment and screening tools**

- Scale of pain LANSS
- Neuropathic Pain Questionnaire
- Questionnaire DN4

**Clinical assessment of neuropathic pain**

- Compression, dislocation, stretching of: (peripheral nerves, nervous roots, plexes, neuretse, cerebral centres)
- Neoplastic infiltration (sensitive nervous structures)
- Iatrogenic causes (neuropathy caused by anticancer treatments: drugs, RT, surgery)

**Neuropathic pain?**

- Yes
  - Non opioids +/- Strong opioids +/- Amitriptyline 25-75 mg/day or Gabapentin 300-3600 mg/day
- No
  - Reassess neuropathic component in mixed pain or search neuropathic mimicking pain
  - Assess neuropathic pain due to bone metastases
TRICYCLIC ANTIDEPRESSANTS

- Blocks the presynaptic re-uptake of serotonin and noradrenaline in the CNS, enhancing the action of the descending inhibitory pathways
- 2 classes:
  - Tertiary amines (amitriptyline, imipramine, doxepin, clomipramine)
  - Secondary amines (nortriptyline, desipramine)
- Amitriptyline: start low dose at night and titrate accordingly
- If intolerable adverse effects/no benefit in one week then consider stopping the drug
ANTICONVULSANTS

- Chemical analogue of GABA (but not GABA receptor agonist)
- Reduces calcium influx in hyper-excited neurones
- No good evidence that more effective than TCAs
- No direct comparator studies
- Caution in renal impairment
- Common side effects: gastric intolerance (nausea and vomiting), sedation, ataxia, dizziness and confusion
  - Gabapentin: 300 - 1200 mg tds
  - Pregabalin: 75mg - 300mg bd
MEDICAL CANNABIS

- Endocannabinoids have regulatory role through nervous system, immune system and elsewhere making them potential therapeutic target
- Current prescribable cannabinoids contain psychoactive component THC/synthetic analogue
- Lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain
- Licensed in the UK for chemo induced nausea and vomiting, refractory spasticity in MS and childhood epilepsy
- More research needed!


ITDD: fewer catheter problems, smaller doses, less adverse effects, better pain control and reduced infection risk

Not appropriate if infection, coagulopathy, short life expectancy

LE>6 mths and trial of temp epidural/spinal
NERVE BLOCKADE

- Peripheral nerve blocks rarely principle pain management
- Neurolytic blocks:
  - 3-6 mths relief
  - Eg. Superior hypogastric plexus (pelvic/perineal); celiac plexus (pancreatic)
END OF LIFE

- Consider alternative route of administration
- Maybe accompanied by other symptoms: dyspnoea, agitation, delirium and anxiety
- May require sedation
- Multidisciplinary team approach
DELIRIUM
EPIDEMIOLOGY

- Incidence in advanced cancer varies: reported to be up to 88% in terminal phase
- Underdiagnosed
- Hypoactive subtype commonest
- Combined physician/nurse assessment best
- Majority of studies: admissions to PCU
- Limited published information on frequency in oncology out-patients
- Mismatch with caregivers’ reports
OUTCOMES

Increased:

- Post discharge mortality
- Institutionalisation
- Rehabilitation needs
- Pressure sores
- Aspiration pneumonia
- Higher rates of:
  - Care home admission
  - Functional decline
  - Readmission
RISK FACTORS

- Baseline vulnerability:
  - Visual impairment, severity of illness, pre-existing cognitive impairment, dehydration
- Precipitating factors or insults:
  - Direct or indirect
  - Cancer related factors, treatment toxicities, physical complications, medications
ASSESSMENT

- **Diagnostic tools**
  - Reference standard DSM/ICD: requires expertise and time
  - Confusion assessment method (CAM): widely used but evidence limited for use in cancer patients

- **Routine:**
  - **Screening**
    - Insufficient evidence in cancer patients but recommend daily observation: impaired concentration, slow responses, withdrawal, sleep disturbances, hallucinations, confusion, agitation, restlessness or mood changes
  - **Monitoring**

- **Collateral history**

1. Acute onset and fluctuating course
2. Inattention
3. Disorganised thinking
4. Altered level of consciousness

**CAM + if 1+2+3/4**
RATING SEVERITY

- Insufficient evidence:
  - MDAS: Memorial delirium assessment scale
  - DRS: delirium rating scale

10-item, 4-point clinician rated scale
Score of 13 = delirium

16-item clinician-rated scale with 13 severity items and 3 diagnostic items
MANAGEMENT

- 20-50% delirium episodes are reversible in advanced cancer
- Medication vs organ failure/hepatic encephalopathy
- Assess capacity nb fluctuating nature
  - Advance care directives
  - Surrogate decision maker
COMMON SCENARIOS

- Polypharmacy
- Opioid toxicity: rotation/switching
- Dehydration: limited evidence to support artificial hydration – case by case basis
- Potentially reversible infections
- Hypercalcaemia: hydration, bisphosphonates, denosumab
- SIADH: review medications, restrict fluid intake, vasopressin receptor antagonists
- Hypomagnesaemia
- Anticancer treatments
## NON-PHARMACOLOGICAL INTERVENTIONS

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<tr>
<th>Targeted Patient-related Risk Factor for Delirium</th>
<th>Strategy</th>
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| Cognitive impairment                              | Reorientation of patient by staff and family  
Explain where they are, who they are, who you are, and your role  
Use orientation white board, visible clock  
Use cognitive stimulating activities, e.g. reminiscence  
Avoid frequent room changes |
| Visual impairment                                 | Use eyeglasses and other visual aids |
| Hearing impairment                                | Use hearing aids or other portable amplifying devices  
Ensure ears are free of impacted wax |
| Immobility                                        | Encourage active range-of-motion exercises for all patients  
Encourage mobilisation as allowed by patient’s performance status, providing walking aids if needed  
Avoid unnecessary urinary catheterisation  
Avoid using physical restraints |
| Dehydration                                       | Encourage patient to drink, provided they can swallow safely  
Assist patient at mealtimes if necessary |
| Sleep-wake circadian cycle disturbance           | Daytime: Increase exposure to daylight whenever possible, discourage napping during the day  
Evening: Warm, non-caffeinated drinks, relaxing music at bedtime, minimise light, noise and disruptions during the night |
PHARMACOLOGICAL INTERVENTIONS

- Cerebral imbalance between excess of dopaminergic and deficiency of cholinergic transmission
- Opioid rotation/switching
- 2nd generation anti-psychotics (less EPSEs):
  - Olanzapine
  - Aripiprazole
  - Quetiapine
- Benzodiazepines: sedation/anxiolysis nb terminal phase
OTHER CONSIDERATIONS

- Experiential impact
- Informational and support needs of family
- Educational needs of healthcare professionals
- Assessing mental capacity:
  - Mental capacity or lack of capacity is something that is decided on a “decision by decision” basis
    - Recognises that some decisions are more complex than others
    - Always assume that someone has mental capacity, and the ability to make specific decisions for themselves
    - If a person lacks mental capacity then a “best interests” (least restrictive) decision is made which should include taking into account:
      - Known past and present wishes, feelings, beliefs and values
      - Views of people who care about the person
TERMINAL AGITATION
TERMINAL AGITATION & SEDATION

- Palliative sedation
  - Intentional lowering of the level of the patients consciousness in order to treat refractory symptoms
- Reverse the reversible!
- Non-pharmacological
  - Quiet, unchanging environment
  - Low level lighting
  - Maintain communication and contact
  - Music therapy

Why variations in practice?
- Philosophy about a good death
- Beliefs about effect of sedation on survival
- Medical practice
- Experience
- Religious practice
- Levels of burnout
ADVERSE OUTCOMES FROM TERMINAL SEDATION

- Side effects of medications
- Loss of interactional function
- Distress amongst families and members of professional team
  - Sadness due to impaired ability to interact
  - Anticipatory grief
  - Confusion or disagreement re: indications
  - Perception that
    - Decision was precipitous or delayed
    - Might directly or indirectly hasten death
10 ITEM FRAMEWORK

1. Pre-emptive discussion with patients (contingency planning)
2. Describe indications
3. Describe necessary evaluation and consultation procedures
4. Specify consent with pt and significant others
5. Indicate need to discuss with family
6. Present direction for selection of sedation method
7. Present direction for dose titration, monitoring and care
8. Guidance for decision regarding hydration, nutrition and concomitant meds
9. Care and informational needs of patient and family
10. Care for medical professionals

European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care

Cherny et al
Palliative Medicine 23(7) 581-593
RECURRENT ASCITES
ASCITES

Obstruction of lymphatic drainage

Cytokine release eg. VEGF, VPF, IL-6, TNF

Accumulation of fluid

Activation of renin-angiotensin-aldosterone system
DIURETIC THERAPY

- 1 RCT (n=68), 3 cohort studies (n=43) and 1 case report (n=2)
  - Diuretic use inconsistent
  - Weak evidence assessing efficacy
  - Overall success ~ 43% cases (based on 5 studies)
  - Interval between initiation and response poorly defined
  - Phase II data: response may depend upon plasma renin/aldosterone concentration
PARACENTESIS

- Temporary relief for 90% patients (Smith et al, 2003)
- Complications:
  - Hypovolaemia
  - Hypoproteinaemia
  - Bowel perforation
  - Infection
  - Formation of drainage nodules
  - Peritoneocutaneous fistulae
  - Pain
MANAGEMENT OF DRAINAGE FOR MALIGNANT ASCITES IN GYNAECOLOGICAL CANCER

Keen, A. et al

- Benefit and harms of different practices in the management of drains for malignant ascites in advanced or recurrent gynaecological cancer.
- Evidence re:
  - How long should the drain stay in place?
  - Should the volume of fluid drained be replaced intravenously?
  - Should the drain be clamped to regulate the drainage of fluid?
  - Should any particular vital observations be regularly recorded?
- No relevant studies were identified
- Unable to make recommendations
- Large, multi-centre RCTs are required to evaluate the efficacy and safety of the management of ascitic drains when in situ and their impact on QOL.

Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007794
PARACENTESIS CONT.

- Stephenson et al (2002)
  - Variation in practice between local hospice and hospital, in relation to:
    - Prior USS
    - Use of IV fluids
    - Length of time drains left in (hospital>hospice)
    - Length of inpatient stay (hospital<hospice)
    - ...ALL hospital > hospice
  - Clinical guidelines drawn up:
    - Prior USS only if ascites not easily clinically identified or signs of bowel obstruction present
    - IV fluids only if patient at risk of hypovolaemia
    - Free drainage of 5L or for 5 hours – whichever is sooner
• Findings:
  ◆ Procedure repeated more frequently in post-guidelines group, *BUT*
  ◆ No significant difference in mean volumes drained
  ◆ No cases of symptomatic hypotension in post-guidelines group
  ◆ Significant reduction in:
    ◆ number of prior USS
    ◆ Mean time drain left in
    ◆ Mean duration of patient stay
• *BUT* are hospital patients more at risk of complications…
INDWELLING PERITONEAL CATHETERS
PLEURX PERITONEAL CATHETER DRAINAGE SYSTEM

- Prevents air entering and fluid leaking
- Encourages tissue growth to secure catheter
PLEURX DRAIN IN MANAGEMENT OF MALIGNANT ASCITES: SAFETY, COMPLICATIONS, LONG-TERM PATENCY, FACTORS PREDICTIVE OF SUCCESS

Tapping, CR et al.

- 28 consecutive patients (4y period, 32 drain insertions, mean age 61y)
- 4 inserted with combination of fluoroscopic and ultrasound guidance and 28 under ultrasound guidance alone
- 100% technical success rate
- No procedure-related deaths/major complications
- Minor complications were reported:
  - Three (10%) immediate; three (10%) early; and two (7%) late.
  - Factors associated: chemo, low Hb/albumin, high WBC, high c-reactive protein
- Length of time the drains in situ: 5 to 365 days (mean, 113 days)
  - 24 (86%) in situ and functioning until the patients' death
  - 4 (14%) drains dislodged but drains remained patent until the patient's death
REVIEW OF OBJECTIVES

- Cancer pain
- Delirium
- Terminal agitation
- Recurrent ascites