Complex Symptom Management at the End of Life of Pediatric Patients

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Impact of Symptoms

• “Parents who felt that their child’s final day was overdue often referred to their child’s extreme overt suffering, and their child’s survival for longer than the parent thought was humanly possible.”

• “More than 10% of bereaved parents considered hastening their child's death. This was more likely if the child was in pain.”
Symptom Burden as the disease progresses

Multiply relapsed cancer

Increasing Symptom Burden

Health Status

Time

Decline

Crises

Death

Goals of care

Cure

“Aggressively Prolong life”

“Comfortably Prolong life”

Comfort

Morbidity

High

Moderate

Mild

Minimal

Psychological attitude

Win

Fight

Live with it

Embrace

Tumor effect

Eradicate

Response

Arrest growth

None

Hope

Hope

Hope

Hope

Symptoms to discuss

- Bone pain
- Bowel obstruction
- Nausea and vomiting
- Delirium
- Anorexia-Cachexia
- Death

Bone pain

- MP – 5 yo female with MB
- Home on hospice
- Long distance management
- Symptom of greatest concern – pain
- Location – legs, back and skull/headache
WHO Analgesic Ladder

- Oral administration when possible
- Dosing at regular intervals
- Prescribing based on intensity (step-wise approach)
- Tailored to the individual

- Not applicable to pure neuropathic pain
- Codeine and other “weak opioids” no longer recommended

Bone pain

- Bone pain is a frequently occurring problem
  - May be constant at rest
  - Much worse with movement

- It is frequently the result of mechanical changes due to metastases, compression or pathologic fracture, etc.

- Cord compression should always be considered when there is significant back pain in the patient with metastatic cancer
Bone metastasis

- Pain can be due to:
  - Direct invasion of bone
  - Microfractures
  - Increased pressure on endosteum
  - Distortion of periosteum
  - Nerve root compression
  - Muscle spasm in area of lesion
  - Increase in release of chemical mediators → nociceptive impulses to the CNS (peptides, prostaglandins, substance P)

Mercandante and Fulfarro. Curr Opin Oncol 2007
Treatment of Bone Pain

• NSAIDs/corticosteroids
• Opioids
  – Methadone
• Invasive Techniques
  – Epidural analgesia
  – Intrathecal analgesia
  – Nerve blocks
• Radiation therapy
• Bisphosphonates
• Radioisotopes
• Orthopedic procedures

NSAIDS and steroids

• May help as adjuvant to opioid therapy (thought not ideal as monotherapy for severe pain)

• Work to attenuate the sensitization of peripheral nociceptors which may decrease prostaglandin synthesis

• How and when do you use steroids?
Opioid Therapies

“Among the remedies which it has pleased Almighty God to give man to relieve his sufferings, none is so universal and so efficacious as opium”
Sydenham, 1680

Opioids

- Three types of receptors
  - Mu (analgesia, most adverse effects)
  - Delta (spinal analgesia, reduced gut motility, dysphoria)
  - Kappa (peripheral analgesia, sedation, dysphoria)

- Mechanism of action
  - Close calcium channels on presynaptic neurons (decrease release of pain-inducing neurotransmitters)
  - Open potassium channels on postsynaptic neurons (inhibits responsiveness to neurotransmitters)
Opioid Therapy

• The main problem with incident pain is not that opioids are not effective, rather that the doses required produce undesirable effects such as sedation.

Methadone

• Long-acting, very effective for chronic pain relief
• Less tolerance (NMDA receptor blocker)
• Fewer side effects
• Addresses neuropathic as well as nociceptive pain
• No active metabolites – safe in hepatic or renal insufficiency

• High oral bioavailability (85-90%)
• Long half-life (12-36 hours)
• Onset of analgesia 30-60 minutes
• Duration of analgesia 4-6 hours → 8-12 hours
Methadone

- Difficult to dose correctly, cannot titrate quickly
- Requires more careful monitoring
- More complicated equianalgesic dosing
- Metabolized through the p450 hepatic enzyme system (CYP3A4, CYP2B6, CYP2C19)
  - Levels increased by SSRIs, “Azol” antifungals, macrolide antibiotics, grapefruit juice, nifedipine, TCAs
  - Levels decreased by carbamazepine, phenytoin, phenobarbital, rispiridone
- Causes prolonged QT interval in at-risk individuals (ECG recommended)

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### Methadone

- Starting dose (opioid naïve): 0.05-0.1 mg/kg/dose (2.5-5 mg PO q6-12 hours)
- Conversion ratio depends on previous total opioid needs

<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>&lt; 100 mg</td>
<td>3:1</td>
<td>20%-30%</td>
<td>33%</td>
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<tr>
<td>101-300 mg</td>
<td>5:1</td>
<td>10%-20%</td>
<td>20%</td>
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<td>301-600 mg</td>
<td>10:1</td>
<td>8%-12%</td>
<td>10%</td>
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<tr>
<td>601-800 mg</td>
<td>12:1</td>
<td>5%-10%</td>
<td>8%</td>
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<tr>
<td>801-1000 mg</td>
<td>15:1</td>
<td>5%-10%</td>
<td>7%</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>20:1</td>
<td>&lt;5%</td>
<td>5%</td>
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</table>
Methadone

• For breakthrough pain
  – 10% of daily methadone, dosed q2-4 hours PRN
  – Previous short-acting opioid (morphine, hydromorphone)
• Converting to IV: 80% of oral dose, same interval
• Can be given as a continuous infusion with PCA

<table>
<thead>
<tr>
<th>Previous Opioid</th>
<th>Basal (per hour)*</th>
<th>New Opioid</th>
<th>Basal (per hour)</th>
<th>PCA bolus q15 min</th>
<th>Clinician Activated Bolus</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>Methadone</td>
<td>1 mg</td>
<td>1 mg</td>
<td>5 mg</td>
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<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>Methadone</td>
<td>0.3 mg</td>
<td>0.3 mg</td>
<td>5 mg</td>
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<tr>
<td>Fentanyl</td>
<td>250 mcg</td>
<td>Methadone</td>
<td>1.25 mg</td>
<td>1.25 mg</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

*Decrease hourly methadone dose by 25-50% for high previous opioids (e.g. >50 mg/hr morphine) and increase by 25-50% for low previous opioids (e.g. 5 mg/hr morphine)

Manfredi and Houde, 2003, J Support Oncol

Invasive analgesia

• Nerve block

• Epidural

• Intrathecal
  – Implantable device

Nerve block and epidural

• Excellent/Improved pain control
• Few complications
• Did not preclude death at desired location
• Able to be placed despite “contraindications”

Limiting factors and contraindications at the time of catheter insertion

<table>
<thead>
<tr>
<th>Case</th>
<th>Device type</th>
<th>ANC (x10^3/L)</th>
<th>Platelet count (x10^3/L)</th>
<th>Other contraindications</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>5300</td>
<td>283</td>
<td>T12 fracture, spinal metastases, fever</td>
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<tr>
<td>2</td>
<td>NB</td>
<td>8300</td>
<td>362</td>
<td>Spinal metastases</td>
</tr>
<tr>
<td>3.1</td>
<td>NB</td>
<td>6300</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>3.2</td>
<td>E</td>
<td>nd</td>
<td>94</td>
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</tr>
<tr>
<td>3.3</td>
<td>E</td>
<td>4600</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>E</td>
<td>2100</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>E</td>
<td>4100</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NB</td>
<td>1300</td>
<td>89</td>
<td>Large wound in targeted area</td>
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<tr>
<td>7.1</td>
<td>E</td>
<td>6300</td>
<td>477</td>
<td></td>
</tr>
<tr>
<td>7.2</td>
<td>E</td>
<td>22300</td>
<td>488</td>
<td>Fever</td>
</tr>
<tr>
<td>8</td>
<td>E</td>
<td>5800</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>E</td>
<td>5400</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>10.1</td>
<td>E</td>
<td>4500</td>
<td>76 (tx)</td>
<td></td>
</tr>
<tr>
<td>10.2</td>
<td>E</td>
<td>4800</td>
<td>106 (tx)</td>
<td></td>
</tr>
</tbody>
</table>

E, epidural; NB, nerve block; ANC, absolute neutrophil count; nd, not done; tx, value after transfusion(s).
Radiation Therapy

• 20% of all radiation therapy is delivered for palliation of bone metastases

• Indications for radiotherapy include:
  – Pain
  – Risk for fracture
  – Risk for spinal cord compression
  – Nerve root pain
  – Cranial nerve involvement
  – Other functional issues

• Goal of XRT not always well understood by patients and families

Bisphosphonates

• Zoledronic Acid = Zometa, Reclast
• Not approved in pediatric patients
• Dose = 4 mg I.V. every 3-4 weeks
• Approved in adults for use in treatment of:
  – Hypercalcemia of malignancy
  – Multiple myeloma
  – Bone metastasis in solid tumors
  – Osteoporosis
  – Paget’s disease of bone
Bisphosphonates

• Mechanism of action: direct inhibition of osteoclast activity and therefore bone resorption

• Binds with high affinity to hydroxyapatite in mineralized bone

• When osteoclasts are stimulated, bisphosphonate is released and internalized by osteoclasts, inhibition of osteoclast formation and induction of osteoclast cell death

Radioisotopes

• Useful for widespread, painful bone metastasis
  – Cochrane Review 2011

• Should not be used for localized areas of disease where external beam radiation would be preferred
Radioisotopes

• Should be considered if
  – Multiple sites of bone pain
  – Metastatic cancer
  – Pain control with conventional analgesia is not satisfactory

• AND
  – Activity of lesion is demonstrated on bone scan

Radioisotopes

• Can have pain “flare” post this therapy
  – Can last 1-5 days

• Can see mild thrombocytopenia, neutropenia (10-30% of patients)
  – Still less likely than with wide field external beam radiation
  – Adverse effects common

• Samarium as example
  • J Pall Med 2004; 7(6): 865-7
  • Lancet Oncology 2005; 6:353-4
Orthopedic procedures

Our patient – MP Pain Regimen

• IT regimen: Dilaudid – 0.35 mg/hr
• Methadone 50/50/50
• Lidocaine patches prn
• Apply diclofenac 1% gel to the right knee and back up to 4 times during the day as needed for pain
• Ketorolac 8 mg IV q 6 hrs prn during pain crises
Symptoms to discuss

- Bone pain
- Bowel obstruction
- Nausea and vomiting
- Delirium
- Anorexia-Cachexia
- Death

Bowel obstruction
Clinical picture

• Colicky abdominal pain
• Abdominal distension
• Vomiting
• Decreased passage of stool or flatus

• Typical radiographic picture
Pathophysiology

• Hypercontractility—hypocontractility
• Massive third space losses
  – Oliguria, hypotension, hemoconcentration
• Electrolyte depletion
• Bowel distension
  – Increased intraluminal pressure
  – Impedement in venous return
  – Arterial insufficiency

Important Questions

• Site
• Etiology
• Partial vs. complete
• Simple vs. strangulated
• Fluid & electrolyte status
• Operative vs. non-operative management
Management – establish goals

• Goals of Treatment
  – The goals of treatment include relieving nausea and vomiting, allowing oral intake, alleviating pain, and permitting the patient to return to their chosen care setting
  – Although it is recognized that improvement in quality of life after surgery is variable (42-85%), there is no consistent parameter used to determine this clinical outcome
  – Operations may offer an advantage of an increased survival

Medical management

• Opioids and anti-emetics
  – Usually dopamine antagonists to relieve nausea

• Antimuscarinic/anticholinergic drugs (e.g. atropine, scopolamine) are used to manage colicky pain due to smooth muscle spasm and bowel wall distension
  – Scopolamine is only available in the US as the hydrobromide salt
  – Penetrates the CNS
  – Potential for significant side effects such as delirium
  – Glycopyrrolate, a quaternary ammonium antimuscarinic with similar clinical, less CNS effects