Advanced Therapies for the Treatment of Cancer Pain
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Introduction

• 2012 more than 1.6 million diagnosed cancer
  • ACS, 2012
• 75% to 90% can have pain controlled
  • Zech, Grond, Lynch, Hertel, & Lehmann, 1995
• 10% to 20% do not achieve pain relief from
  WHO three-step ladder approach
  • White & Rajagopal, 2006

Introduction

• Four types of cancer pain
  – Nociceptive somatic
  – Nociceptive visceral
  – Neuropathic
  – Mixed
• Reasons to consider advanced techniques
  – Poorly controlled pain
  – Medication side effects
  – Need to reduce systemic medications
  – Likely need for pain control as disease progresses
Introduction

- Not new techniques
  - Routine at beginning of 20th century
- Choice based on life expectancy
  - Provide relief several days, weeks, months, or years depending on therapy used

Intrathecal Drug Delivery System (IDDS): History

- 1899: Dr. August Bier performs cocainization of the spinal cord
- 1973: opioid receptors identified on spinal cord
- 1979: first time intrathecal morphine used for cancer pain
- 1985-1990: Medtronic developed intrathecal pump

IDDS: Anatomy

- 5 opioid receptors in CNS
  - MU, Kappa, Delta, Sigma, Epsilon
- Nociceptive input modulated in spinal cord
- Intrathecal opioids passively diffuse into dorsal horn of spinal cord
  - No anatomic barriers
  - Vascular absorption slow
  - Drug concentrated close to site of action
IDDS: Patient Selection
• Diagnosis cancer: somatic or visceral
• Failed systemic opioids or intolerable side effects
• Minimum life expectancy 3 months
• Positive trial
• No uncontrolled coagulopathies
• No acute infection
• Able to be off chemotherapy short-term
• Aplastic anemia absolute contraindication
• Early in course of disease
  • Dennis, & Day, (2012)

IDDS: Procedure
• Local + sedation or GA* or spinal
• Tuohy needle to access intrathecal space
  – L2-L3, L3-L4, or L4-L5
• Catheter threaded to appropriate level
• Pump pocket
• Catheter tunneled and attached to pump
• Pump filled and programmed

Creating the pump pocket
IDDS: Patient Management

- FDA approved agents
  - Morphine
  - Ziconotide
  - Baclofen
- General conversion
  - Intrathecal dose is 1/100 to 1/300 of parenteral dose
  - Not an exact science

IDDS: Patient Management

<table>
<thead>
<tr>
<th>First Line Agents</th>
<th>Second Line Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Morphine or Hydromorphone + Ziconotide</td>
</tr>
<tr>
<td>Ziconotide</td>
<td>Morphine or Hydromorphone + Bupivacaine +/‐ Clonidine</td>
</tr>
</tbody>
</table>

**IDDS: Patient Management**

- Basal rate +/- PTM (patient therapy manager)
- Wear abdominal binder 2-4 weeks post implant
- Can be refilled as little as every 3 months once pain stable
- Adjustments made using external programmer

**IDDS: Risk vs Benefit**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical procedure</td>
<td>Reduced incidence opioid side effects</td>
</tr>
<tr>
<td>Infection</td>
<td>Freedom from pill burden</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Very effective</td>
</tr>
<tr>
<td>Neurological injury</td>
<td>Ability to use multiple agents</td>
</tr>
<tr>
<td>CSF leak</td>
<td>Targets pain at site of transmission</td>
</tr>
<tr>
<td>Catheter dislodgement or fracture</td>
<td>Longer survival, improved quality of life, reduced pain compared to standard medical management</td>
</tr>
<tr>
<td>Pocket refill</td>
<td></td>
</tr>
<tr>
<td>Programming or refill error</td>
<td></td>
</tr>
<tr>
<td>Inflammatory catheter tip mass</td>
<td></td>
</tr>
</tbody>
</table>

**IDDS: Efficacy**

- Can effectively reduce visceral, somatic, neuropathic and mixed cancer pain
- Pain 10/10 ⇝ 3.5/10
  - Lin, Lin, Lin, Lee, Jeng, & Sun (2012)
- > 80% satisfactory reduction pain and systemic opioid use
  - 45% to 90% excellent
    - Fitzgibbon (2001)
### Midline Myelotomy: History

- 1926: first myelotomy performed
- Many different techniques over the years with a variety of results
- Mechanism of pain relief not fully understood

### Midline Myelotomy: Anatomy

- Target: center of the spinal cord
- Visceral pain pathway deep within dorsal column ascend to higher pain centers
- Spinothalamic fibers and visceral afferents decussate (criss-cross) deep medial dorsal column

### Midline Myelotomy: Patient Selection

- Midline or bilateral visceral pain of abdomen or pelvis not responsive to high dose opioids
  - Rectal
  - Vaginal
  - Perineal
  - Liver
  - Pancreas
  - Ovarian
  - Sacral
Midline Myelotomy: Procedure

- Two methods
  - Open: thoracic laminotomy, open dura, cord transected using direct vision
  - Closed: percutaneous, lesion made in cervical spinal cord with probe

Measuring the spinal cord

Crushing midline of the spinal cord
Cutting the decussating fibers midline spinal cord

Midline myelotomy end result

Midline Myelotomy: Risk vs Benefit

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical procedure</td>
<td>Satisfactory to good relief</td>
</tr>
<tr>
<td>Patient may be in poor condition</td>
<td>Effect may last few years</td>
</tr>
<tr>
<td>No guarantee long-lasting effect</td>
<td>May cover large parts of the body</td>
</tr>
<tr>
<td>Possible areas of sensory loss</td>
<td>Decrease opioid use</td>
</tr>
<tr>
<td>Other side effects: hyperesthesia, impaired proprioception, paresis,</td>
<td></td>
</tr>
<tr>
<td>uncoordinated gait, motor/sphinctor dysfunction</td>
<td></td>
</tr>
</tbody>
</table>
Midline Myelotomy: Efficacy

• Success rate 60% to 70%
  • Giller (2003)
• Data strongly suggests effective procedure for limited subset of cancer patients
• Not considered first line procedure

Percutaneous Anterolateral Cordotomy (PALC): History

• 1912: done for pain from pelvic tumor
• Bilateral PALC prone to complications
  – Impaired respiratory, bowel, bladder, and sexual function
  – Impaired vasomotor control
  – Girdle pain
• Common before advances in cancer pain pharmacotherapy and IDDS

PALC: Anatomy

• Anterolateral quadrant of spinal cord contains ascending pain pathways
• Carries mainly pain and temperature
• SST is very important in pain transmission
• SST diffusely intermingled with other ascending and descending systems
• Fibers organized from outside inward
PALC: Patient Selection
- Unilateral cancer pain at level below C5 dermatome
- Neuropathic and nociceptive pain
- Thoracic malignancy, compression of nerves, and visceral
- Life expectancy up to 2 years
- Contraindications
  - Severe pulmonary dysfunction
  - Unable to lie supine 30-40 minutes
  - pO2 less than 80%

PALC: Procedure
- Laminectomy
  - Done under general anesthetic
  - Spinous processes and lamina removed bilaterally T2-T3 level
  - Microscopic guidance
  - Cordotomy electrode inserted into white matter and lesion made
- Percutaneous
  - Newer method
  - Lower morbidity
PALC Procedure

- Percutaneous
  - Done using CT guidance
  - Monitored airway control sedation
  - Needle placed from lateral neck at C1-2 and passed into anterior cord
  - Lesion made with cordotomy electrode

Using CT scanner to view spinal cord
Needle in correct location anterolateral spinal cord

### PALC: Risk vs Benefit

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful dysesthesias</td>
<td>Substantial to complete relief of pain</td>
</tr>
<tr>
<td>Damage to nearby pathways</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Bowel, bladder, sexual</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral weakness</td>
<td></td>
</tr>
<tr>
<td>Mirror pain</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
</tbody>
</table>

### PALC: Risk vs Benefit

- **n= 2616 patients**
  - Death (0-4.6; mean 3)
  - Respiratory (0-4.6; mean 3.5)
  - Bladder (1.5-15; mean 7.6)
  - Temporary weakness (4-17; mean 7.6)
  - Permanent weakness (0-3; mean 1)
  - Ataxia (0-5; mean 4)
  - Hypotension (0-3.3; mean 2.2)
  - Decreased pain
    - Early (80-96; mean 85)
    - Late (42-75; mean 60)

- Hodge & Christensen, 2002
### PALC: Risk vs Benefit

<table>
<thead>
<tr>
<th>Bilateral</th>
<th>Unilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality up to 50%</td>
<td>Morbidity/mortality 0%-9%</td>
</tr>
<tr>
<td>Respiratory dysfunction 40%</td>
<td>Respiratory dysfunction 0%-5%</td>
</tr>
<tr>
<td>Ondine’s curse: failure to breathe when asleep.</td>
<td></td>
</tr>
</tbody>
</table>

Kanpolat, Ugur, Ayten, & Elhan, 2009

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### PALC: Efficacy

- **Immediate results**
  - VAS mean 8.5 → 1.2
  - 6 months VAS mean 2.3  
  Raslan (2008)
- **Significant improvement in performance, pain, and hours of sleep**  
  Raslan (2008)
- **Effect rarely lasts beyond 2 years**
- **Can be repeated with good results**

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### Hypophysectomy: History

- **1952:** first reported in America and France
  - Transcranial approach
- **Next two decades, widespread acceptance for end-stage prostate and breast cancer**
- **Control tumor growth and pain**
- **1960s:** transphenoid approach
- **1970s:** focus shifted to palliation of pain
- **Currently:** stereotactic approach
- **Less commonly used today**
Hypophysectomy: Anatomy

- Surgical destruction or removal of pituitary gland
- Do not know how this results in relief of pain

Hypophysectomy: Patient Selection

- Opioid refractory cancer pain secondary to bony metastases
- Weeks to months to live

Hypophysectomy: Procedure

- Done chemically and surgically in the past
  - Severe adverse effects
    - Diabetes insipidus and visual dysfunction
- Gamma knife
  - Adverse effects of past not noted
Gamma knife

Patient ready to undergo gamma knife

Hypophysectomy
Hypophysectomy: Risk vs Benefit

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes insipidus</td>
<td>Rapid, short-term complete to near complete resolution of pain within 24-36 hours</td>
</tr>
<tr>
<td>CSF rhinorrhea</td>
<td></td>
</tr>
<tr>
<td>Pan-hypopituitarism</td>
<td></td>
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<tr>
<td>Hypothalamic injury</td>
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<tr>
<td>Ocular palsy</td>
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<tr>
<td>Visual field loss</td>
<td></td>
</tr>
<tr>
<td>Carotid puncture</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

Hypophysectomy: Efficacy

- Significant reduction of pain in 6/6 with cancer pain within 7 days
- Pain relief despite progression of disease
- Effect lasts up to 11 months

Cingulotomy: History

- 1962: first performed in psychiatric patient
- Does not relieve pain per se but reduces emotional component of pain
Cingulotomy: Anatomy

- Cingulate gyrus lies on medial surface cerebral hemisphere
- Fibers arising from anterior CG spread widely in multiple directs
- Complex network of limbic and non-limbic pathways
- Coordinates sensory input and emotions/emotional response to pain

Cingulotomy

Cingulotomy: Patient Selection

- Pain anywhere in body
  - Nociceptive not neuropathic
    - Bone metastases or visceral pain
- Failure of standard therapies
- Not candidate for IDDS
- Pain associated with anxiety, depression, prominent emotional lability and suffering
- Suffering caused by aspiration, choking, dysarthria or respiratory problems intertwined with pain
Cingulotomy: Patient Selection

- Not for acute pain
- Not for persons with pronounced hysterical or sociopathic personality

Cingulotomy: Procedure

- Stereotactic
  - Minimally invasive
  - Avoids problems associated with larger cranial openings
  - 30 to 45 minutes long
  - Local with IV sedation
  - Bilateral lesioning of CG

Bilateral cingulotomy target area
### Cingulotomy: Risk vs Benefit

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Significant or meaningful improvement</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>Effect lasts months</td>
</tr>
<tr>
<td>Fever</td>
<td>No deaths reported</td>
</tr>
<tr>
<td>Transient bladder dysfunction</td>
<td></td>
</tr>
<tr>
<td>Isolated seizure</td>
<td></td>
</tr>
<tr>
<td>Transient unsteady gait, dizziness, mild confusion</td>
<td></td>
</tr>
<tr>
<td>Rarely intracranial hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

### Cingulotomy: Efficacy

- n=15 patients with cancer pain
  - 67% meaningful reduction in pain at one-month
  - Decreased to 58% at 3 months
  - Decreased to 50% at 6 months
    - Yen, Jung, Su, Lin, Howing, & Kwan (2005)
- Effect lasts up to 1 year
- Does not control newly developed pain

### TR-NC: History

- 1938: first performed for trigeminal neuralgia but never caught on
- 1989: percutaneous method developed using CT guidance
- Today referred to as Trigeminal tractotomy-trigeminal nucleotomy (TR-NC)
TR-NC: Anatomy

- Trigeminal afferents carrying pain and temperature send descending branch into medulla
- Cranial nerves 7, 9, 10 also enter descending tract
- Fibers terminate in spinal trigeminal nucleus which has 3 distinct subdivisions:
  - Nucleus caudalis plays special role in pain relief
TR-NC: Patient Selection

- Pain of the face, head, neck, or upper body from orofacial and skull based neoplasm
- Severe pain on coughing, chewing, or swallowing

TR-NC: Procedure

- MRI preoperatively
- Myelogram and CT guidance
- MAC sedation
- Needle inserted at C1 occipit level
- Target is descending trigeminal tract and nucleus caudalis
- Lesion created by heating electrode
  - Cannot be bilateral
- Relieves pain on opposite side of body

TR-NC
TR-NC: Risk vs Benefit

<table>
<thead>
<tr>
<th>Risk</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary or permanent ataxia</td>
<td>High efficacy</td>
</tr>
<tr>
<td>Transient dysesthesia</td>
<td>Low complication rate</td>
</tr>
<tr>
<td>Oculomotor dysfunction</td>
<td>Minimally invasive</td>
</tr>
</tbody>
</table>

Conclusion

• Application of newer techniques and modern technology to older well established neurosurgical procedures has the very real potential for reducing or eliminating intractable cancer pain through utilization of minimally invasive, safe, and effective procedures.