Topics

Significance

Current treatment approaches

General pain mechanisms

Pain related to specific conditions

Chemotherapy

Pancreatic cancer

Bone cancer

• IASP launches global year (10/08-10/09) against cancer pain. “Raise awareness, improve treatment, grow support”.
• > ten million people are diagnosed with cancer each year.
• ~ 30% of adults receiving treatment and 66% with advanced malignant disease experience pain.
  – Head and neck (67-91%)
  – Prostate (56-94%)
  – Uterine (30-90%)
  – Genitourinary (58-90%)
  – Breast (40-89%)
  – Pancreatic (72-85%)
With increasing survival and length of treatment, treatment-related chronic pain issues arise:

- Post-surgery pain, amputations
- Anti-estrogen therapy-related musculoskeletal pain
- Opioid-induced hyperalgesia
- Drug induced peripheral neuropathies
- Need to identify treatments that are effective in reducing pain and improving quality of life of patients that now live longer.

Therapy is typically multi-modal.

**Table 1: Therapies used to treat cancer pain**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>antidepressants, anticonvulsants, and tricyclics</th>
<th>opioids</th>
<th>radon</th>
<th>DMG</th>
<th>Local anesthesia</th>
<th>Thoracic interventions</th>
<th>Intra-tumoral instillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory</td>
<td>Pro-inflammatory molecules facilitate pain transmission.</td>
<td>Tumor and associated immune cells release endothelin, cytokines, prostaglandins, TNF-α, growth factors (NGF) and protons, which excite primary afferents.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nociceptors exhibit afferent and efferent functions.
1. Respond to inflammatory milieu; transmit pain.
2. Nociceptor activation causes release of substances from terminals that cause plasma extravasation, activation of immune cells, vasodilation.

**Pain in Cancer - General Mechanisms**

**Neuropathic pain - cancer infiltration**
- Tumor infiltration of nerve tissue can cause neuropathic pain (and cancer spread).
- Cancer cells can entrap nerves or invade mechanically sensitive tissues.
  - Stretching of hollow viscera, distortion of solid organ capsule, and mucosal inflammation and ischemia or necrosis activate visceral nociceptors.

Preclinical models suggest pain in different types of cancer is driven by mechanisms and factors unique to the disease.

Response to therapy dependent on disease. NSAIDs or COX-2 inhibitors can be effective initially in bone cancer, but are less so for pancreatic cancer pain.

Is need to define molecular mechanisms that underlie the various cancer conditions and tailor treatments to the biology that are effective and have fewest side effects.
Chemotherapy induced peripheral neuropathy

Pancreatic cancer pain

Bone cancer pain

Chemotherapy induced peripheral neuropathy

- Side effect of chemotherapeutics in the taxane (taxol, paclitaxel), vinca alkaloid and platinum-complex classes.
- Affects 25-50% of patients.
- May resolve in weeks/months or last for years.
- Leading cause of therapy discontinuation; significant impact on patients’ quality of life.

What are underlying mechanisms that cause neuropathies/pain?
What is the best pharmacologic approach for treatment of CIPN?
Rat model - paclitaxel (taxol) infusion

Taxol infusion increases ATF3 expression, abnormal NFs and activated macrophage infiltration of the DRG.


Chemotherapy induced peripheral neuropathy - damage is cumulative.

Nodule of nageotte - remains of neuron and satellite cells. Found in human as well.

Bennett group - taxol induced neuropathic pain is due to mitochondrial damage that damages distal endings.

Paclitaxel delivered IP.

Saph nerve and number of microtubules ok.

Mechanical sensitivity (allodynia, hyperalgesia) develops.

Mitochondria in c fiber and myelinated fibers were swollen and vacuolated - effect may be through Ca++ dysregulation.
Mantyh vs Bennett results: Difference in response to taxol may be due to IV administration and rich vascularization of DRG. Lack of blood-nerve barrier.


Taxol rat model

Produces mechano- and cold allodynia, mechano-hyperalgesia; little or no heat hyperalgesia.

Pharmacology - Bennett lab used repeated dosing paradigm (4 daily IP injections) to test effectiveness of drug classes on allodynia/hyperalgesia.

Reduces mechanical sensitivity

Inconsistent action


Antidepressants (with repeated dosing) were effective. Support clinical data that show tricyclics help some patients. Anti-epileptics, sodium (mexiletine) and calcium channel blockers (NMED126) also effective.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemotherapy Dose</th>
<th>Symptoms Affected</th>
<th>Dose &amp; Route</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Channel Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Channel Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-LOX inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-LOX inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cathepsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cathepsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antidepressants (with repeated dosing) were effective. Support clinical data that show tricyclics help some patients. Anti-epileptics, sodium (mexiletine) and calcium channel blockers (NMED126) also effective.
Topamax - enhances GABA-activated Cl channels; inhibits AMPA and kainate receptor; protects against mitochondrial membrane damage.

Direct analgesic effect coupled with recovery of epidermal nerve terminal, perhaps due to effect on mitochondria.

NSAIDs - no effect; MK-801- no effect; opioid effect mixed.

Overall, most promising - amitriptyline, tramadol and topiramate.

Need for clinical validation.
Factors in pancreatic pain:
- Inflammation, neuroimmune interactions.
- Elevated pancreatic pressure
- Ischemia
- Tissue hypoxia and acidosis
- Increased release/activation of proteases.
- Increased macrophages
- Increased NGF from tumor and macrophages.
- Perineural invasion by tumor cells.

- Normal
- Enlarged nerve in pancreatitis
- Perineural invasion of tumor cells
- Endoneural invasion

Inflammation
- Sensory/sympathetic sprouting
- Neovascularization


Table 1. Expression of neuropeptides in chronic pancreatitis (CP) and pancreatic cancer (PC) and their influence on pain.

<table>
<thead>
<tr>
<th>Neuropeptide</th>
<th>CP</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIP (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPY (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEP (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HTP (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPV1 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPA1 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCK-8 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIP (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPY (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEP (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HTP (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPV1 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPA1 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCK-8 (7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NTs lead to nerve hypertrophy, neural density and induce pain in pancreatitis/cancer.

Supports the idea that nerves provides a microenvironment for growth and metastasis of cancer cells.

TRPV1 sensitization in primary afferents may lead to inflammation-induced acute hyperalgesia.
Current pancreatic cancer pain treatments
- Celiac nerve block - alcohol injection
- Radiation and/or chemotherapy
- Insertion of drug-delivery pumps
- Narcotics
- NSAIDS/anti-depressants/anti-convulsants

Future therapies??
- Block trkA kinase (k252a reduced pain in rat model).
- Anti-NGF molecule?

Bone Cancer Pain
- Metastatic spread of cancer to bone - most common cause of pain in human cancer.
- Ongoing, spontaneous breakthrough and movement-evoked pain due to bony metastases; increase with disease progression.
- Difficult to control - has inflammatory (macrophage), neuropathic and tumorigenic components.
- Sensory neurons that innervate the bone marrow cause pain from osteoclast and osteoblast activity that lead to osteolysis and fractures.

Bone cancer pain mouse model (Mantyh, 1999) - osteosarcoma tumor cells injected into the femur produce bone destruction.
- Behavior - indicative of ongoing and movement-evoked pain.
- Pain resistant to opioid therapy; requires 10-fold higher doses of morphine compared to inflammatory pain.
- Likely to have neuropathic/tumorigenic component given resistance to opioids.

Radiograph shows progressive loss of bone in medullary canal and distal femur due to tumor growth.
Distal processes of sensory fibers in the marrow are injured by invading tumor.

Current pain therapies (morphine) have unwanted side effects; sedation, constipation, mental clouding, particularly in the elderly.

New therapies under development:

- Osteoprotegerin (OPG) - secreted soluble receptor (TNFR family) that prevents the proliferation of osteoclasts by sequestering osteoprotegerin ligand (OPGL or RANKL).
  - Decreases pain behaviors.
  - Increases bone density; reduces osteoclasts.


...and an anti-NGF molecule.
NGF sequestering antibody blocks binding of NGF to trkA and p75 receptors.
NGF modulates inflammatory and neuropathic pain states and is expressed by tumor, inflammatory and immune cells.

Anti-NGF had no effect on disease progression.
No difference in pattern of tumor growth/bone destruction.

No difference in sensory innervation of skin.

Anti-NGF attenuates bone cancer pain.
Anti-NGF reduced pain more efficiently than morphine at 10 or 30 mg/kg given 15 min prior to testing.

Anti-NGF:

Reduced expression of ATF3 and infiltration of CD68-IR macrophages in the L2 DRG.

Decreased ?? dynorphin-IR in neurons in deep lamina.

Anti-NGF aka Tanezumab (RN624) - humanized monoclonal antibody given IV

In Phase 2 trial for pain associated with bone metastases.

Phase 2 clinical trials for endometriosis pain.

Phase 3 trials for knee and hip pain due to osteoarthritis.

Placebo - 15.5% decrease in walking pain

Tanezumab - 32.1% decrease in pain.

Side effects- headache (8.9%), upper respiratory tract infections (7.3%) and paraesthesia (6.8%).