MANAGING SHORT AND LONG-TERM SIDE EFFECTS OF CHEMOTHERAPY

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Agenda

- Clinical Context
  - Chemotherapy-Induced Nausea and Vomiting (CINV)
  - Hormone-Related Symptoms
  - Chemotherapy-Induced Peripheral Neuropathy (CIPN)
  - Bone Health
  - Cardiotoxicity
  - Preventative Health

Objectives

1. Describe the management of side effects associated with the treatment of breast cancer
2. Identify the most common chemotherapy drugs used to treat breast cancer that cause peripheral neuropathy and the treatment options for chemotherapy-induced peripheral neuropathy (CIPN)
3. Become familiar with preventative health approaches for patients with breast cancer
CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN)
Description, pathophysiology, risk factors, prevention, & treatment

CIPN: description
• A condition caused by chemotherapy drugs that results in damage to the peripheral nerves
• Is typically dose-dependent and cumulative
• Symmetric “stocking and glove distribution” - numbness, tingling, loss of sensation, feeling of “pins and needles”, burning, discomfort/pain
• Onset: during treatment (acute) to months-years after completion of chemotherapy (“coasting”)

CIPN: pathophysiology
Three types of peripheral nerves:
• Autonomic: internal organs
• Motor: muscles & motion
• Sensory: affect sensation
CIPN: risk factors

- Type of chemotherapy: platinum agents (carboplatin, cisplatin), taxanes (paclitaxel, nab-paclitaxel, docetaxel), eribulin, ixabepilone, vinorelbine
- Prior radiation and surgery: can cause damage to peripheral nerves, which can lead to neuropathy
- Pre-existing conditions: diabetes, peripheral vascular disease, HIV/AIDS, folate deficiency, older age
- Tumor pathology: direct compression of nerves

CIPN: prevention - exercise

Exercise:

- Secondary analysis of a Phase III randomized controlled trial (RCT) including 314 patients receiving chemotherapy
- Moderate-intensity, progressive, 6-week walking & resistance program vs no exercise
- Exercise reduced CIPN w/ older pts benefiting more
- Many other benefits of exercise and no major risks

CIPN: prevention - supplements

Omega 3 Fatty Acids:

- RCT including 57 pts with breast cancer receiving paclitaxel
- Pts received omega-3 TID during and for 1 month after chemo
- Incidence of CIPN in pts taking omega-3 was 30% vs 59% in the placebo group
- ASCO: inconclusive evidence to recommend for or against
CIPN: prevention - supplements

Vitamin E:
- RCT including 207 patients treated with platinum or taxane
- No difference in incidence of neuropathy, time to onset, or need for chemotherapy dose reduction
- ASCO: vitamin E should not be recommend for the prevention of CIPN


CIPN: pharmacologic treatment

Duloxetine (Cymbalta):
- RCT including 231 patients with taxane or platinum-associated CIPN
- 59% of pts who received duloxetine had a decrease in pain vs 38% of pts who received placebo
- Pts who received duloxetine had a larger decrease in average pain score than those who received placebo
- Dose: 30 mg daily x 1 week, then 60 mg daily thereafter
- Side effects: headache, drowsiness, fatigue, nausea, dry mouth
- Avoid in patients taking tamoxifen


CIPN: pharmacologic treatment

- Anticonvulsants: gabapentin, pregabalin
- Antidepressants: nortriptyline, amitriptyline, venlafaxine
- Topical agents: lidocaine, capsaicin, baclofen/amitriptyline/ketamine (BAK) gel
- Opioids

CIPN: complementary treatment

- Physical therapy, occupational therapy
- Acupuncture - small case series show benefit
- Transcutaneous nerve stimulation (TENS)
- Massage

Side effects of anti-estrogen therapy

Vasomotor symptoms, arthralgia/myalgia, & vaginal dryness

Hormonal Therapy: mechanism of action & side effects

- Tamoxifen: selective estrogen receptor modulator (SERM) that competitively binds to estrogen receptors on tumors and other tissues to inhibit estrogen effects
- Aromatase Inhibitors (AIs): inhibit the enzyme aromatase, which converts androgens into estrogens
- Side effects of low estrogen: vasomotor sx., vaginal dryness, thinning/loss of hair, decreased bone density, arthralgias, and myalgias
**Hormonal Therapy: vasomotor sx.**

- Recurring transient episodes of flushing and sweating, with a sensation of heat, often accompanied by palpitation or anxiety, and sometimes followed by chills
- Occur in ~ 20-40% of patients
- Breast cancer survivors are 5.3 times more likely than women in the general population to experience hot flashes

**Non-pharmacologic treatment**

- Acupuncture
- Exercise/physical activity:
  - 150 minutes moderate-intensity or 75 minutes of vigorous activity per week
  - Strength/resistance training 2 to 3 times per week
  - Stretch major muscle groups 2 days per week
- Lifestyle modifications:
  - Smoking cessation, limit EtOH, avoid caffeine
  - Weight loss if overweight
  - Dress in layers, cotton clothing and bedding, fans, cooling aids

**Antidepressants:**

- Venlafaxine (Effexor) - preferred
- Desvenlafaxine (Pristiq)
- Escitalopram (Lexapro)
- Citalopram (Celexa)
- Sertraline (Zoloft)*
- Paroxetine (Paxil)*
- Fluoxetine (Prozac)*

**Anticonvulsants:**

- Gabapentin (Neurontin) - preferred
- Pregabalin (Lyrica)

**Antihypertensive:**

- Clonidine (Catapres)
**Hormonal Therapy: myalgias/arthralgias**

- **Drug Causes:** taxanes, ixabepilone, AI > tamoxifen
- **Risk factors:** age, prior chemotherapy, hx of arthritis, arthralgia, or fibromyalgia

<table>
<thead>
<tr>
<th></th>
<th>Aromatase Inhibitors</th>
<th>Tamoxifen</th>
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<tbody>
<tr>
<td>Prevalence of arthralgia</td>
<td>18.6% - 25.6%</td>
<td>11.8% - 29.4%</td>
</tr>
<tr>
<td>Median time to onset</td>
<td>13.9 months</td>
<td>17.7 months</td>
</tr>
<tr>
<td>Prevalence of myalgia</td>
<td>21%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

- **Mild symptoms:**
  - lifestyle changes (exercise, weight loss)
  - Heat, cold pack, PT, massage, acupuncture, yoga
  - Pharmacotherapy: APAP, NSAI, Tramadol, Codeine + APAP, muscle relaxants

- **Moderate to severe symptoms:**
  - Drug holiday? Switch AI to tamoxifen? Alternative AI?
  - Pharmacotherapy: NSAI, opioid combination, pain modifiers (TCAs, gabapentin, pregabalin, SNRI), articular steroids

**Hormonal Therapy: vaginal dryness**

- **Non-hormonal therapy:**
  - Vaginal moisturizers, gels, oils, topical Vitamin D or E
  - Lubricants for sexual activity

- **Hormonal therapy:**
  - Local estrogen tx (rings, suppositories, creams)
    - Rings & suppositories preferred over creams
BONE HEALTH
Pathophysiology, cause of bone resorption, screening & monitoring, & treatment

Bone Health: pathophysiology
- Osteoclasts breakdown bone and osteoblasts form new bone
- Estrogen increases the activity of osteoblasts and supports bone remodeling
- Low estrogen = skeletal fragility

Bone Health: causes of low BMD
- Naturally occurring bone loss
- Bone loss in patients on cancer therapies

Photo: shecares.com; 2019
Bone Health: screening & monitoring

- All patients with cancer who are at increased risk for bone loss because of therapy and/or age
- DXA scan: used to determine bone mineral density
  - complete every 24 months if at elevated fracture risk
- FRAX: tool utilized to estimate fracture risk


Bone Health: prevention of bone loss

Nonpharmacologic Recommendations:
- Weight-bearing exercise & physical activity
  - 30 min per day of moderate intensity exercise
- Tobacco cessation & limiting alcohol
- Maintain adequate dietary intake of Calcium & Vitamin D
  - Women 51 years and older: 1,200 mg calcium
  - Calcium carbonate: take with food
  - Calcium citrate: okay to take w/o food
  - Women 19 to 49 years: 400-800 IU vitamin D
  - Women 50 years and older: 800-1000 IU vitamin D


Bone Health: prevention & treatment of bone loss

Pharmacologic Recommendations:
- Bisphosphonates: used for prevention and treatment
  - AI-induced bone loss: zoledronic acid 4 mg every 6 months x 5 years
  - Postmenopausal osteoporosis: zoledronic acid 5 mg once a year x 3-6 years
  - Prevention of postmenopausal osteoporosis: zoledronic acid 5 mg every 2 years
- Denosumab: FDA approved for treatment only
  - AI-induced bone loss: denosumab 60 mg every 6 months
  - Postmenopausal osteoporosis: denosumab 60 mg every 6 months

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)
Pathophysiology, pharmacologic and non-pharmacologic methods of management

CINV: What is it?
- Nausea and vomiting induced by chemotherapy agents
- The goal is PREVENTION
- Risk of CINV can be anticipatory, acute, or delayed and is affected by the specific chemotherapy agent
- Risk factors:
  - Younger age (less than 50 years)
  - Women
  - Low alcohol use
  - History of motion sickness
  - History of morning sickness


CINV: Pathophysiology
- Nausea and vomiting occur as a result of signals occurring in the brain
- Anti-nausea medications block these signals in different ways
  - Effective treatment for CINV often results from a combination of medications
    - Variety of mechanisms

### CINV: Risk and Chemotherapy

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Emetic Risk</th>
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<tbody>
<tr>
<td>ddACT (doxorubicin, cyclophosphamide, paclitaxel)</td>
<td>High</td>
</tr>
<tr>
<td>TCH/TCHP (docetaxel, carboplatin, trastuzumab, ± pertuzumab)</td>
<td>High</td>
</tr>
<tr>
<td>TC (docetaxel, cyclophosphamide)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Xeloda (capecitabine)</td>
<td>Minimal to Low</td>
</tr>
<tr>
<td>Ibrance (palbociclib)</td>
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**Non-Pharmacologic Management**

- Take anti-nausea medications early and often as prescribed
- Eat small, bland meals throughout the day
- Avoid spicy foods
- Maintain adequate hydration
- Relaxation methods
- Ginger

**CINV: Risk and Treatment**

- **High risk (>90%)**
  - 3-4 drug regimen (steroid, serotonin antagonist, NK1 antagonist, zolanzapine)
  - Continued for 3 days after chemotherapy
- **Moderate risk (30% - 90%)**
  - 2-3 drug regimen (steroid, serotonin antagonist)
  - Continued for 2 days after chemotherapy
- **Low risk (10% - 30%)**
  - Single drug regimen - given once prior to treatment
- **Minimal risk (<10%)**
  - As needed drugs only

Pharmacologic Management

- Dexamethasone
- Serotonin receptor antagonists
  - Ondansetron (Zofran®)
  - Palonosetron (Aloxi®)
  - Granisetron (Kytril®)
- Neurokinin (NK1) antagonists
  - Aprepitant/fosaprepitant(Emend®)
  - Rolapitant (Varubi®)
  - Netupitant/palonosetron (Akynzeo®)
- Olanzapine (Zyprexa®)
- Prochlorperazine (Compazine®)

Pharmacologic Management (cont’d)

- Dexamethasone
  - Mechanism of action: Unknown for CINV
  - Side effects
    - Increased blood glucose
    - Edema
    - Insomnia
  - Pearls
    - For extended delayed CINV, course of dexamethasone can be extended
    - Take in the morning with a meal
    - Increase blood glucose most notable within 48 hours of dexamethasone administration
Pharmacologic Management (cont’d)

- Ondansetron (Zofran®)
  - Mechanism of action: Serotonin receptor antagonist
  - Side effects
    - Headache
    - Constipation
    - QTc prolongation
  - Pearls
    - Palonosetron is a good alternative if QTc prolongation is a concern
    - Most effective with scheduled administration
    - Bowel regimen for patients taking scheduled ondansetron

Pharmacologic Management (cont’d)

- Netupitant/palonosetron (Akynzeo®)
  - Mechanism of action
    - Netupitant: Neurokinin antagonist
    - Palonosetron: Serotonin receptor antagonist
  - Side effects
    - Headache
  - Pearls
    - Effects last for ~72 hours
    - Additional serotonin antagonist should not be given within 72 hours
    - Both ingredients are effective at decreasing delayed nausea

Pharmacologic Management (cont’d)

- Olanzapine (Zyprexa®)
  - Mechanism of action: Antipsychotic, serotonin/dopamine receptor antagonist
  - Side effects
    - Sedation
    - Restless leg syndrome (RLS)
  - Pearls
    - 5 mg dose may be effective if 10 mg causes excessive sedation/RLS
    - Sedation is greatest on day 2 and improves over time
    - Can be substituted for dexamethasone for patients intolerant to dexamethasone
Pharmacologic Management (cont’d)

- Prochlorperazine (Compazine®)
  - Mechanism of action: Dopamine receptor antagonist
  - Side effects
    - Sedation
    - Seizure
  - Pearls
    - Most effective when used at the first sign of nausea onset
    - Can be taken at the same time as ondansetron and olanzapine
    - Also available as a suppository

CARDIOTOXICITY

Mechanism of cardiotoxicity, common chemotherapy agents involved, and management

Cardiotoxicity: What is it?

- Cardiotoxicity: “Toxicity that affects the heart”
- A condition caused by chemotherapy - presentation can vary from asymptomatic to life-threatening
- Can be acute, subacute, or chronic
- Symptoms: Heart failure, arrhythmia, asymptomatic
- Risk factors include older age (>60 years), compromised heart function, treatment
Cardiotoxicity: Chemotherapy Agents

- Trastuzumab (Herceptin®)
- Anthracyclines
  - Doxorubicin (Adriamycin®, Doxil®)
  - Epirubicin (Ellence®)
- Varying mechanisms and presentations of cardiotoxicity

Cardiotoxicity: Mechanisms and Presentations

<table>
<thead>
<tr>
<th></th>
<th>Anthracycline-like</th>
<th>Trastuzumab-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular mechanism</td>
<td>Cell death</td>
<td>Cell dysfunction</td>
</tr>
<tr>
<td>Dose related</td>
<td>Cumulative</td>
<td>Non-cumulative</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Permanent</td>
<td>Reversible</td>
</tr>
<tr>
<td>Presentation</td>
<td>Years after treatment; HF</td>
<td>Weeks after treatment; HF</td>
</tr>
</tbody>
</table>

Cardiotoxicity: Management

- Early use of cardioprotective agents is an area of ongoing investigation
  - ACE inhibitors
  - Beta-blockers
  - ARBs
  - Statins?
- Several studies have indicated that early initiation of cardioprotective agents may be helpful in recovering cardiac function and providing cardioprotection
Cardiotoxicity: Management (cont’d)

- Dexrazoxane (Zincard®)
  - For doxorubicin-induced cardiomyopathy in metastatic breast cancer (>300 mg/m²)
  - ASCO: For patients who will receive high-dose anthracyclines and may benefit from further anthracycline treatment
  - Studies show that use decreases the risk of heart failure without decreasing effectiveness of treatment

PREVENTATIVE HEALTH

Immunizations - importance, safety, timing

Immunizations: Importance

- Cancer patients are at increased risk of infection
  - Immunosuppressive therapies
  - Malignancy itself
- Influenza
  - Mortality due to influenza infection ranges from 9% to 33%
  - Lower rates of respiratory disease, hospitalization, and mortality with vaccination
Immunizations: Concerns

- Risk of disease

- Efficacy
  - Vaccines require a healthy immune system to be effective
  - Inactivated vaccines administered during chemotherapy should not be considered valid doses unless protective antibody level documentation


Immunizations: Which are safe?

- All inactivated vaccines can be safely administered to immunocompromised persons
- Most immunocompromised persons should not receive live vaccines
- Severe complications have resulted from vaccination with certain live vaccines (viral and bacterial)

Centers for Disease Control and Prevention. Vaccine Recommendations and Guidelines of the ACP.

Immunizations: Inactivated vs. Live

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Inactivated</th>
<th>Live</th>
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<tbody>
<tr>
<td>Influenza</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Flu-mist</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tdap</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Zostavax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shingrix</td>
<td>✓</td>
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**Immunizations: When?**

- Preferred: Prior to planned treatment initiation

- Inactivated vaccines
  - At least 2 weeks before or 3 months after treatment

- Live vaccines
  - At least 4 weeks before treatment or at least 3 months after treatment (physician should be consulted)
  - Should be avoided during chemotherapy

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**Immunizations: Influenza**

- All breast cancer patients (≥6 months) should receive the *inactivated influenza vaccine* (IIV) annually

- Flu-Mist (nasal, live influenza vaccine) should not be given to immunocompromised patients

- In addition to prior to chemotherapy start, the IIV may be given between chemotherapy cycles

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CINV: Pathophysiology - Central

- Delayed nausea (>24 hours)
- Leads to chemoreceptor trigger zone and vomiting center
CINV: Pathophysiology - Peripheral

- Acute nausea (0-24 hours)
- Leads to chemoreceptor trigger zone and vomiting center

Immunizations: Pneumococcus

- Pneumococcal vaccine should be administered to all newly diagnosed adults with breast cancer (PCV13, followed by PPSV23)
- Should be given at least 2 weeks prior to the start of chemotherapy

Immunizations: Herpes Zoster

- If vaccination can occur at least 4 weeks before immunosuppressive therapy:
  - Should be given to patients ≥60 years if it can be administered at least 4 weeks before immunosuppressive therapy
  - Should consider for varicella-positive patients 50-59 years of age
- Recommendations for Shingrix pending
### Immunizations: Varicella

- Should be given to immunocompromised patients without evidence of immunity if it can be given at least 4 weeks before immunosuppressive therapy
- 2-dose schedule (separated by >4 weeks) in adults if there is sufficient time prior to chemotherapy initiation
- Should not be administered to highly immunocompromised patients


### Immunizations: Close Contacts

- Close contacts of patients being treated for breast cancer can safely receive inactivated vaccines based on CDC-ACIP recommendations
- Annual influenza vaccine is strongly recommended (inactivated or live)
- Additional recommended vaccines: MMR, varicella, zoster