The Good, The Bad, and The Ugly of Hormonal Therapy, Trastuzumab and Docetaxel

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Presenter Disclosure

- Speaker: Diane Johnson
- Relationships with commercial interests: None

Mitigating Potential Bias

Not Applicable

Learning Objectives

1. List the common toxicities of hormonal agents, trastuzumab and docetaxel

2. Describe side effect management strategies for hormonal agents, trastuzumab and docetaxel

3. Consult useful references and patient information resources

Case: Patient E.J.

- 49 y.o. female with breast cancer
  - T2N2 → Chemo
  - ER/PR positive → Hormonal therapy
  - HER2 positive → Trastuzumab
- Treated with FEC-D x 6 cycles
- Seen in clinic prior to cycle # 5 docetaxel

Docetaxel - The Good

- Very effective chemotherapy for adjuvant and metastatic disease

Docetaxel - The Bad

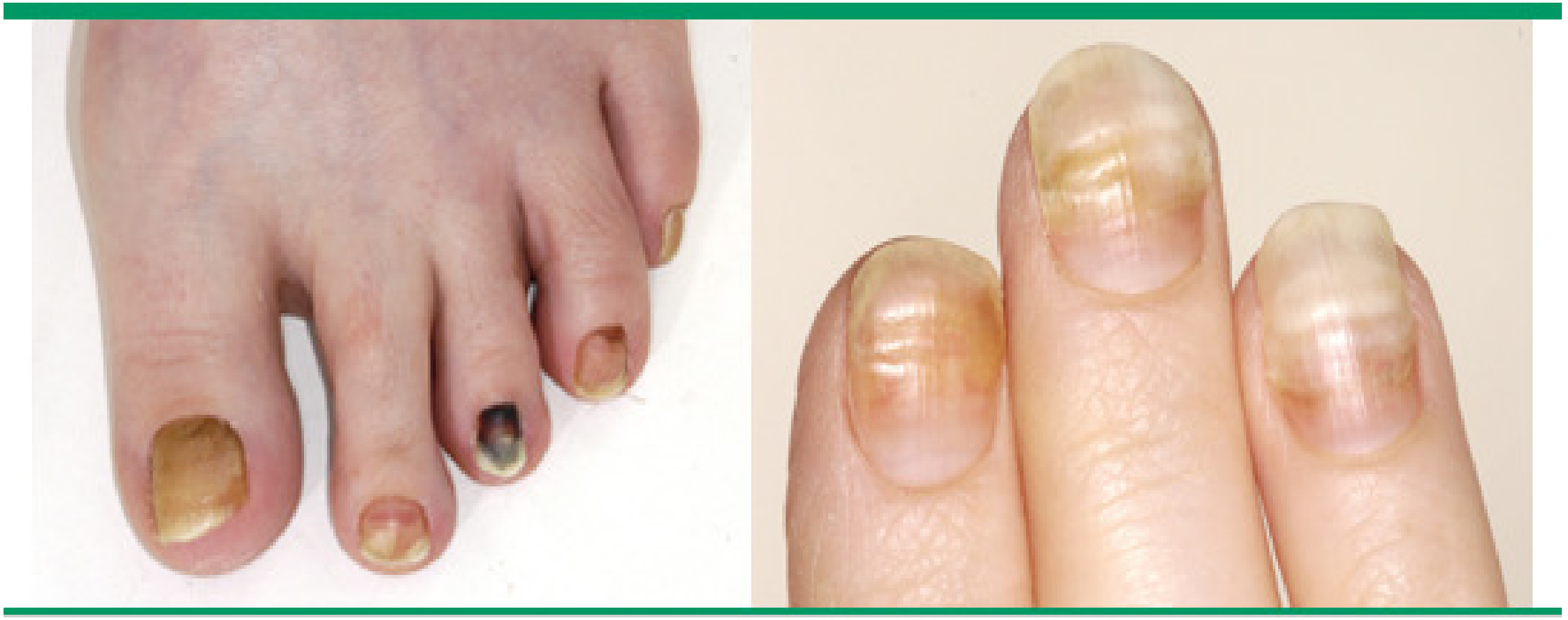
- Many side effects:
  - Neutropenia and risk of infection
  - Fluid retention
  - Hypersensitivity reactions
  - Hair loss
  - Muscle/joint pain

Docetaxel - The Bad

- Peripheral neuropathy
- Skin/nail changes
- Increased liver enzymes and bilirubin
- Tearing/watery eyes

Docetaxel - The Ugly

Nail changes with Docetaxel



Courtesy of Dr. Elaine Sugden. Graphic 63373 Version 3.0 ©2015 UpToDate

Docetaxel

- Some side effects may take a long time to resolve after stopping treatment (e.g. months)
  - Most are slowly reversible
  - Rarely permanent

Case: Patient E.J.

- Seen in clinic prior to cycle # 5 docetaxel:
    - Experienced significant muscle pain in legs for about 3-4 days after cycle # 4 docetaxel
    - Also had a rash on arms and body
- What can we suggest for E.J.?

Muscle/joint pain

- Usually transient
- Occurs within a few days after docetaxel administration
- Lasts about 4 days

Management:

- Usually respond to mild analgesics (e.g. acetaminophen or NSAIDs)
- If not helpful, could try gabapentin or acetaminophen with codeine

Skin reactions

- Rash on hands, feet, arms, face, thorax
  - With or without itching
  - Occurs within one week
  - Resolves before next infusions

Management:

- Symptomatic
  - Emollients
  - Topical corticosteroids
  - Cooling compresses
  - Antihistamines

T2N2, ER/PR positive, HER2 positive

Case: Patient E.J.

- Seen in clinic prior to cycle # 5 docetaxel:
  - Muscle pain → acetaminophen
  - Rash → betamethasone cream and diphenhydramine
  - Start trastuzumab
- Seen prior to cycle # 6 docetaxel
  - LFTs increased
  - Peripheral neuropathy – numbness and tingling in feet
- What do we do?

Docetaxel Toxicity Management

Dosage with Hepatic Impairment:

	AST/ALT		**Alk Phosp**		**Bilirubin**	**Docetaxel Dose**
Mild-moderate	> 1.5 X ULN	AND	> 2.5 x ULN			75%
Severe	> 3.5 x ULN	AND	> 6 x ULN	OR	> ULN	Do not treat. Discontinue if treatment already started.

https://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=10760

If liver enzymes elevated dose adjustment may be required – **verify with oncologist**

Peripheral neuropathy

- Dose-related, sensory
- Pain, numbness, tingling in hands/feet
- Usually improves within 9 weeks after stopping docetaxel

Management:

- Anticonvulsants (e.g. gabapentin or pregabalin)
- Tricyclic antidepressants (e.g. amitriptyline, nortriptyline)
- Topical analgesic agents (e.g. capsaicin, lidocaine cream)
- Opioid (short or long acting)
- Corticosteroid

http://www.bccancer.bc.ca/nursing-site/Documents/14.%20Peripheral%20Neuropathy.pdf

T2N2, ER/PR positive, HER2 positive

Case: Patient E.J.

- Seen prior to cycle # 6 docetaxel
  - High LFTs → docetaxel dose decreased to 75 %
  - Trastuzumab continues at same dose (does not require decrease)
  - Peripheral neuropathy → gabapentin 300 mg tid
- Finished chemo
- 6 weeks later
  - Neuropathy getting better
  - Continues trastuzumab q 3 weeks x 1 year
  - Starts tamoxifen

Trastuzumab - The Good

- Generally well tolerated
- Only 30 minute infusion
- No pre-medications
- No bloodwork

Trastuzumab - The Bad

- About 40 % of patients experience an infusion reaction with the first dose
  - Chills
  - Fever
  - Nausea
  - Shortness of breath
- Usually transient, self-limited, and responsive to acetaminophen and supportive care measures
- Infusion reactions very rare after first infusion

Trastuzumab - The Ugly

- Cardiotoxicity – ventricular dysfunction and congestive heart failure in about 2% of patients
  - Responsive to heart failure medical therapy

- MUGA scans required q 3 months

- Note:
  - Dr. Jassal will be presenting on Cardiotoxicity at the Community Cancer Care 2015 Education Conference in October

Tamoxifen - The Good

- Used for many years and lots of experience using it
- Very effective in reducing odds of recurrence and death
- Estrogen antagonist
- May also have cytotoxic activity
- Acts as an estrogen agonist on bone and lipids
  - may prevent bone loss (postmenopausal)
  - lowers total cholesterol (may decrease overall cardiovascular mortality)

Tamoxifen - The Bad

- Hot flashes – common
- Vaginal symptoms - endometrial changes, irregular menses (premenopausal)
- Depression
- Increased risk of cataracts

Drug interactions

- Tamoxifen is converted into its active metabolites by CYP2D6 liver enzyme
- Efficacy may be affected by SSRIs/SNRI's that are strong inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, bupropion)
- If patient on tamoxifen, best to use citalopram, escitalopram, venlafaxine or desvenlafaxine

Tamoxifen - The Ugly

- Serious complications:
  - Endometrial cancer (0.8 %), uterine sarcoma
    - Need routine gynecological monitoring
    - Report any abnormal symptoms such as irregularities, abnormal bleeding or discharge, pelvic pain
  - Blood clots (2-5% risk, severe 1-2 %)

T2N2, ER/PR positive, HER2 positive

Case: Patient E.J.

- Finished chemo
- Continues trastuzumab
- On tamoxifen
- 6 month follow-up
  - Hot flashes

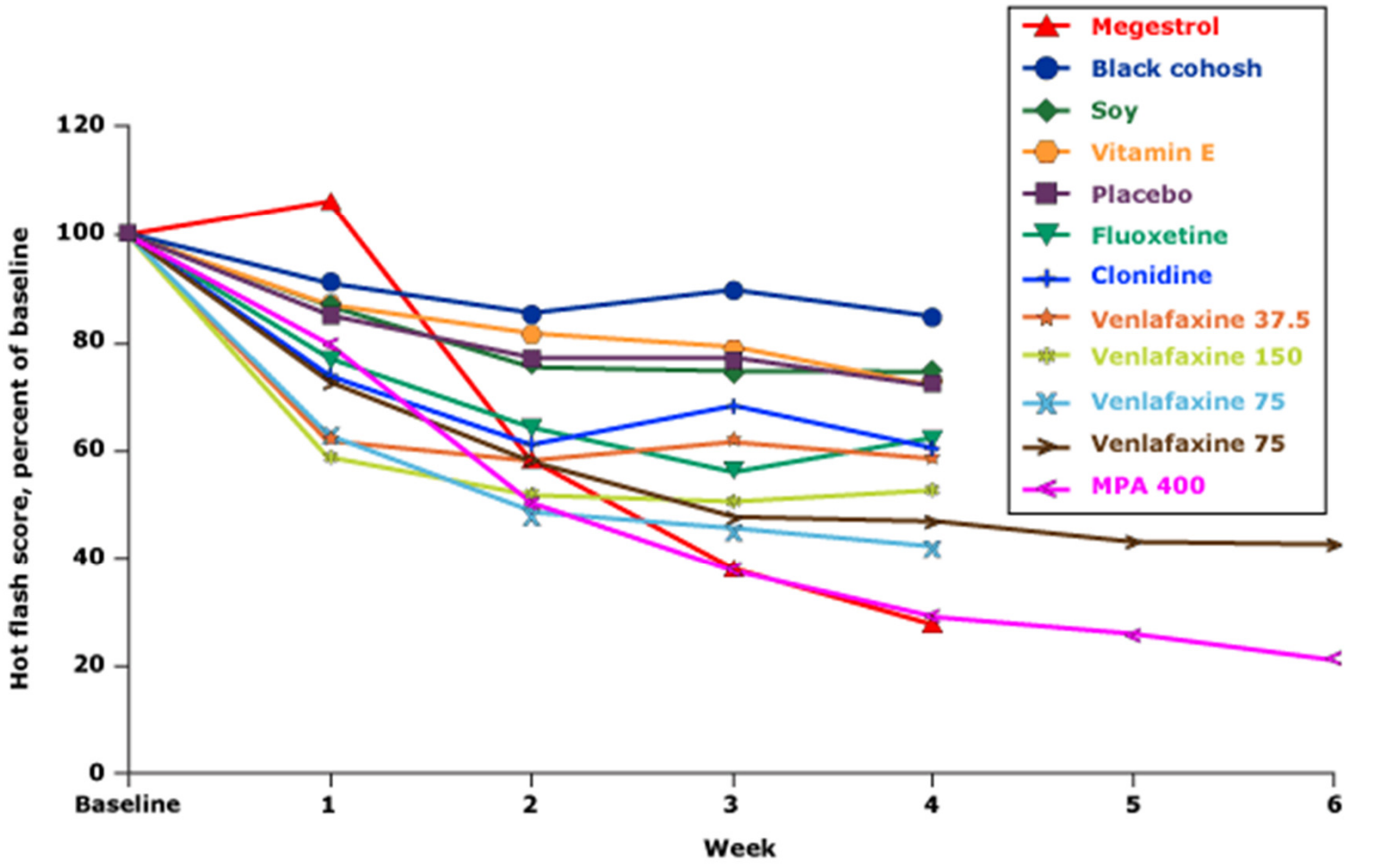
Management strategies

- Hot flushes in day - take at bedtime
- Night sweats - try in AM
- If dampens sleeping cloths, keep a spare set near bed so can easily change and return to sleep comfortably
- Dress in layers - no heavy or thick fabrics
- Use fans
- Weight loss
- Avoid triggers:
  - Caffeine (coffee, tea, colas)
  - Chocolate, spicy foods, hot food and drinks
  - Stress
  - Alcohol, cigarettes
  - Hot weather, hot tubs, saunas, hot showers and rooms

Management Strategies Continued

- SSRIs/SNRIs
  - Venlafaxine, desvenlafaxine
  - Citalopram/escitalopram
  - Paroxetine (but not with tamoxifen)
  - Clonidine
- Gabapentin
- Research is ongoing in the role of soy proteins for symptom control after a diagnosis of breast cancer. Many other treatments are also under investigation.
- Avoid use of: black cohosh, isoflavones and phytoestrogens, red clover (estrogenic properties, no efficacy data)

Therapies hot flashes



http://www.uptodate.com/contents/search?source=USER_PREF&search=hot+flashes+treatment&searchType=GRAPHICS

Case: Patient E.J.

- Been on Tamoxifen for 3 years
- Now 52 y.o.
- Postmenopausal
  - Switched to letrozole

Aromatase Inhibitors – The Good

- Letrozole, anastrozole, exemestane

- Similar efficacy and toxicity for each
- Associated with 3% decrease in breast cancer recurrence at 5 yrs compared to tamoxifen
- Lowers estrogen levels by blocking aromatase enzyme
- Pill taken once per day
- **Only for postmenopausal women

Aromatase Inhibitors – The Bad

- Side effects:
  - Hot flashes
  - Muscle or joint aches or pains
  - Mild headache and diarrhea
  - Bone density loss
  - Vaginal dryness
  - Increased cholesterol and triglycerides

Aromatase Inhibitors – The Ugly

- Osteoporosis (6 %) - fractures
- Increase in CV events (serious MI/stroke)

Osteoporosis Prevention and Treatment:

- Weight bearing exercise
- Calcium – sum consumed from diet and supplements (1200 mg/day total)
- Vitamin D – at least 1000 units per day
- Smoking Cessation
- Avoidance of heavy alcohol use
- Counseling on fall prevention
- Bisphosphonates

- Good reference from BCCA called Patient Guidelines for the Prevention of Osteoporosis in Women

Management of vaginal symptoms:

- Vaginal dryness/irritation: non-hormonal, water-based moisturizers or lubricants (i.e., Replens, Vagisil, K-Y SILK-E)

- If unsuccessful, small amounts of estrogen cream (i.e., 1/4 manufacturer's recommended dose) applied topically, intermittently may be helpful
  - Estrogen used in this fashion is absorbed systemically
  - Potential risks and benefits should be discussed

- Estring (intravaginal estrogen releasing device) - serum levels of estrogen are only apparent for 24 hours after the initial use
  - More local effect with less systemic absorption

- **Need to weigh benefit vs. risk

- http://www.bccancer.bc.ca/books/breast/follow-up/post-menopausal-replacement

Fulvestrant - The Good

- Health Canada Approval:
  - For the hormonal treatment of locally advanced or metastatic breast cancer in postmenopausal women, who have disease progression following prior antiestrogen therapy
- Blocks the estrogen receptor. No ER agonist activity
- Activity against tamoxifen-resistant breast cancers
- No significant interactions

Fulvestrant – The Bad

- Requires Non-formulary approval
- Side effects:
  - Hot flashes
  - Headache
  - Back pain
  - GI (nausea)
  - Elevated liver enzymes

The Ugly

IM injection (two 250 mg/5 mL injections), one in each buttock

https://www.google.ca/search?q=injection+clipart&rls=com.microsoft:en-us:IE-Address&rlz=1I7AURU_enCA498&hl=en&tbm=isch&ei=wx6LVdSCItKlyATguazoBA&start=20&sa=N

Comparison Chart of Hormonal Therapy Side Effects

	Anastrozole	Exemestane	Letrozole	Tamoxifen	Fulvestrant
bone/joint pain	yes	yes	yes		
osteoporosis	yes	yes	yes		
bone thinning	yes	yes	yes		
nausea	yes		yes	yes	yes
vomiting	yes		yes		yes
hot flashes	yes	yes	yes	yes	yes
weakness	yes	yes			
fatigue	yes	yes	yes	yes	
headache		yes		yes	yes
insomnia		yes			

Adapted from http://www.breastcancer.org/treatment/hormonal/comp_chart

Take Home Message

- Variety of possible toxicities and strategies to manage them
- Long duration of treatment with hormonal therapy (5 to 10 years) so important to encourage compliance and monitor for toxicity
- Important to ask patients how they are doing and encourage discussion
- Lots of good references and resources for patients:
  - BC Cancer (bccancer.bc.ca) Cancer Management Guidelines
  - Cancer Care Ontario (cancercare.on.ca)
  - breastcancer.org
  - Calcium Calculator (osteoporosis.ca)
  - UpToDate