Clinical Updates and Issues: Metastatic Breast Cancer

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Mayo Clinic Cancer Center

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Learning Objectives

- Describe the complexities in treating metastatic breast cancer.
- Outline new evidence-based systemic treatment recommendations for patients with metastatic breast cancer.
- Recognize and manage adverse events associated with newer treatment regimens for patients with metastatic breast cancer.

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Overview

- Initial workup for metastatic breast cancer
- Updates in treatment of metastatic
  - Hormone Positive BC
  - Her2 Positive BC
  - Triple Negative BC
- Prevention of Skeletal Related Events (SRE)

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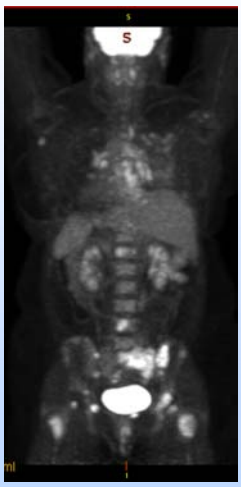
My patient has an abnormal PET/ CT scan, now what?

- 51 y/o with history of T2, N0 ER/ PR+, HER2- BC 2005 (dx at age 41).
- Completed 5 years of adjuvant Tamoxifen in 2010.
- Premenopausal
- Reports new, progressive hip pain.



February 2015

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Audience Response Question

Are you ready to answer?

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My patient has an abnormal PET/ CT scan, now what?

1. Contact Hospice
2. Treat with carboplatin + paclitaxel, 3 weeks on, 1 week off. Plan to restage with PET/ CT in 3-4 cycles.
3. Start on aromatase inhibitor with concurrent goserelin injection with plan to restage with PET/ CT in 3 months.
4. Biopsy concerning lesion

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My patient has an abnormal PET/ CT scan, now what?

- Tissue is the issue
  - ER/ PR/ Her2/ Ki67
  - 15-30% of recurrences will have loss of ER
  - 10-15% will have change in HER2

MAYO CLINIC

Foukakis et al., 2012

Choosing Treatment

- Need to consider
  - Hormone receptor and HER2 status
  - Evidence of visceral crisis
  - Patient goals

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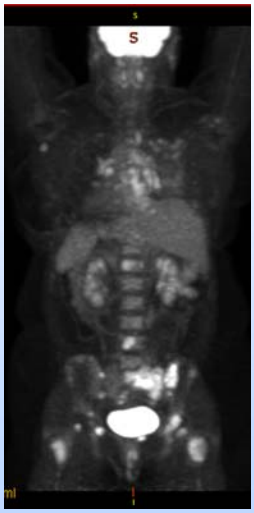
Estrogen Sensitive MBC

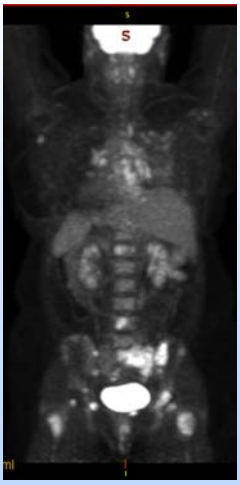
Estrogen Positive MBC

Our patient:

- Premenopausal
- Bone bx
  - ER positive >75%
  - PR positive >75%
  - Her2 negative 1+
  - Ki 67 12%



Estrogen Positive MBC



Treatment Plan:

1. Bilateral salpingo-oophorectomy
2. Started letrozole + palbociclib
3. zoledronic acid 4mg IV q 3 months for prevention of skeletal related events (SRE)

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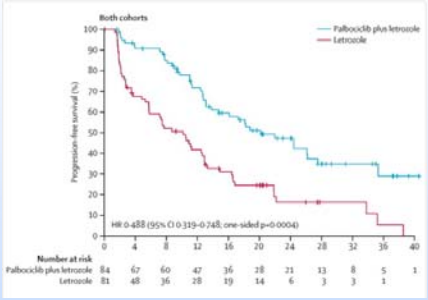
Estrogen Positive MBC

- 1st Line: palbociclib +letrozole
  - PALOMA- 1 trial
    - CDK 4/6 inhibitor
    - Postmenopausal
    - Non steroidal AI vs. non steroidal AI + palbociclib
      - 2.5mg letrozole QD
      - 125mg PO palbociclib 21 days on, 7 off
    - MPFS extended from 10.2 to 20.2 months
    - Study not powered for OS
    - Accelerated approval granted by FDA



Finn et al., 2015

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Audience Response Question

Are you ready to answer?

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Your patient is prescribed palbociclib and letrozole for first line therapy for metastatic estrogen positive breast cancer. You should counsel her on which of the following side effects when considering both medications.

1. Non febrile neutropenia
2. Fatigue
3. Vasomotor symptoms
4. All of the above

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Palbociclib
Nursing Considerations

Most common all-cause adverse events that occurred in at least 10% of patients (safety population)

	Palbociclib plus letrozole (n=83)			Letrozole (n=77)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	19 (23%)	49 (59%)	14 (17%)	49 (64%)	16 (21%)	0
Neutropenia	17 (20%)	40 (48%)	5 (6%)	3 (4%)	1 (1%)	0
Leucopenia	20 (24%)	16 (19%)	0	2 (3%)	0	0
Fatigue	30 (36%)	2 (2%)	2 (2%)	17 (22%)	1 (1%)	0
Anaemia	24 (29%)	4 (5%)	1 (1%)	4 (5%)	1 (1%)	0
Nausea	19 (23%)	2 (2%)	0	9 (12%)	1 (1%)	0
Arthralgia	18 (22%)	1 (1%)	0	10 (13%)	2 (3%)	0
Alopecia	18 (22%)	NA	NA	2 (3%)	NA	NA

… to name a few…

Finn et al., 2015

Palbociclib
Nursing Considerations

- Non Febrile Neutropenia
  - CBC
    - Cycles 1 & 2 days 1 and 14.
    - Day 1 of each cycle.
    - Day 1 & 14 of any cycle with dose adjustment
- Fatigue
  - Cumulative
  - May require dose reduction
- Hair Thinning
  - Anticipatory Guidance
  - Due to arrest of cell cycle
- Drug-Drug Interactions
  - Metabolized through CYP3A pathway
  - Pharmacy consult recommended before initiation

Palbociclib
Dose Adjustments- Non- Hematologic

Table 3. Dose Modification and Management – Non-Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the next lower dose.

Grading according to CTCAE Version 4.0.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf

Palbociclib
Dose Adjustments- Non- Hematologic

Table 1. Recommended Dose Modification for Adverse Reactions

Dose Level	Dose
Recommended starting dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf

Palbociclib
Dose Adjustments- Hematologic

Table 2. Dose Modification and Management[a] – Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3[b]	No dose adjustment is required. Consider repeating complete blood count monitoring one week later. Withhold initiation of next cycle until recovery to Grade ≤2.
Grade 3 ANC (<1000 to 500/mm^3) + Fever ≥38.5ºC and/or infection	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2 (≥1000/mm^3). Resume at next lower dose.
Grade 4[b]	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2. Resume at next lower dose.

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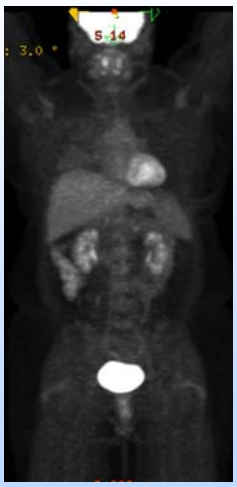
Estrogen Positive MBC



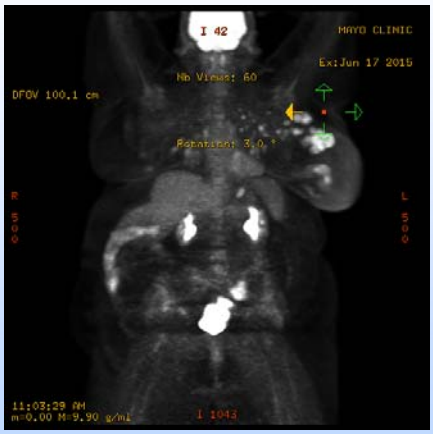
June 2015

"Complete metabolic response of all skeletal and nodal foci."

Patient continues on letrozole + palbociclib to date

Estrogen Positive MBC

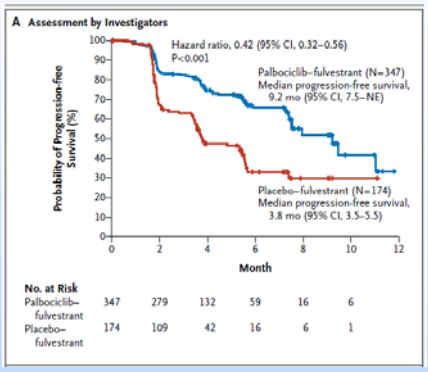
- 54 y/o, premenopausal
- Dx with MBC to lung 2014, ER/ PR +, Her2 –
- Premenopausal
- 2014 Tamoxifen
- 2015 progression of lung mets, new bone and adrenal mets



June 2015

Estrogen Positive MBC

- 2nd line: palbociclib
  - PALOMA- 3 trial
    - CDK 4/6 inhibitor
    - Postmenopausal
    - Fulvestrant (F) vs. F + palbociclib
      - 500mg F C1D1&14, C2D1, then q 28 days
      - 125mg PO palbociclib 21 days on, 7 off
    - MPFS extended from 3.8 to 9.2 months
    - OS data not mature



Turner et al., 2015.

Palbociclib
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Finn et al., 2015

Palbociclib
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Palbociclib
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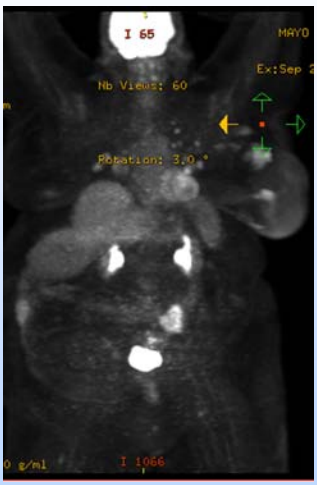
Adapted from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf

Estrogen Positive MBC

Treatment Plan:

1. OFS with goserelin
2. fulvestrant + palbociclib
3. Continued zoledronic acid 4mg IV Q 3 months

Improvement in FDG of skeletal lesions, improvement in size of breast and adrenal lesion, mixed response in pulmonary nodules



September 2015

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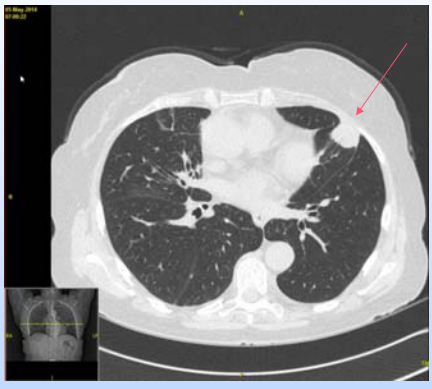
Her2 Positive MBC

HER2 Positive MBC

- 72 y/o
- Dx MBC ER-/PR-, HER2+ to liver, bone, lung, adrenals
- No history of previous BC treatment



May 2014

Audience Response Question

Are you ready to answer?

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HER2 Positive MBC

What would you choose to treat her with first?

1. Paclitaxel weekly 3 weeks on, 1 week off
2. Paclitaxel + trastuzumab (T) weekly for 12 weeks then trastuzumab q3 weeks ongoing
3. Docetaxel+trastuzumab (T)+pertuzumab (P) q 3 weeks for 6 cycles followed by P+T q 3 weeks ongoing
4. Capecitabine 2 weeks on, 1 week off + lapatinib daily

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HER2 Positive MBC

- 1st line: docetaxel (D) + T+ P q 3 weeks x 6, then T+P q3 weeks ongoing
  - Cleopatra: double blind placebo controlled
    - D+T vs D+T+P
      - PFS 12.4 mo vs. 18.5 mo [1]
        - PFS also improved when stratified by neoadjuvant/ adjuvant treatment
      - OS 40.8 mo vs. 56.5 mo [2]

1. Baselga et al., 2012.
2. Swain et al., 2015.

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Docetaxel + Pertuzumab+ Trastuzumab
Nursing Considerations

- Docetaxel [1]
  - 75-100mg/m2
  - Neutropenia
  - Alopecia
  - Capillary Leak Syndrome
  - Neuropathy
  - Nausea
  - ***Diarrhea***
- Dual Anti-Her2
  - Trastuzumab [3]
    - 8mg/ kg C1, 6mg/kg ongoing
    - Acute cardiac failure
    - Fatigue
  - Pertuzumab [2]
    - 840 mg C1, 420mg ongoing
    - ***Diarrhea***
    - Fatigue

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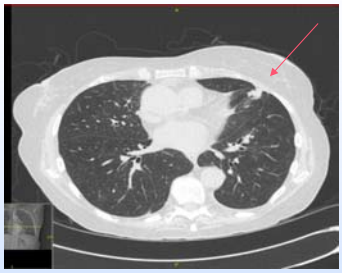
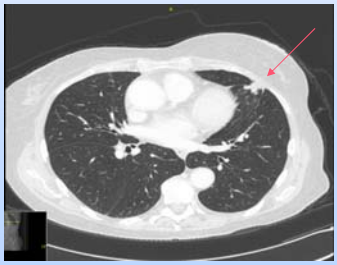
1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020449s059lbl.pdf
2. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125409lbl.pdf
3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf

HER2 Positive MBC

- Treatment complicated by colitis resulting in hospitalization
- Completed 4 cycles before omitting D
- Maintained on T+P for 18 months



July 2014



April 2015

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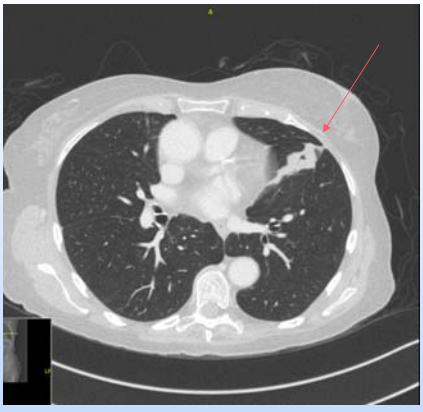
HER2 Positive MBC

- Imaging December 2015
  - Progression in pulmonary metastasis
  - Patient maintaining ECOG 0



What do you do next?

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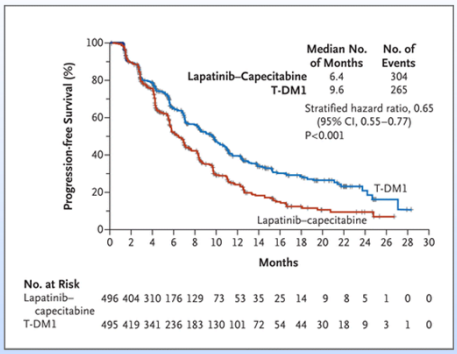
Her2 Positive MBC

- 2nd line: ado-trastuzumab emtansine (T-DM1)
  - EMILIA Trial, Phase III
    - T-DM1 in previously treated Her2+ MBC vs lapatinib + capecitabine
    - Antibody-drug conjugate
      - Trastuzumab bound to emtansine molecules
      - Binds to tubules and prevents microtubule formation
    - PFS 9.6 vs. 6.4 mo
    - OS 30.9 vs. 25.1



Verma et al., 2012

T-DM1
Nursing Considerations

- Infusion reaction: 2% incidence
- Thrombocytopenia ~30% incidence
  - 12% grade 3 or 4 on EMILIA
  - Dose reduce at 25,000 PLTs
- Elevated transaminases
  - Improves with dose reduction
  - Reduce to 3.0mg/kg for AST >3x ULN & Bili >2x ULN per EMILIA
- Cardiomyopathy
  - **Black Box Warning**
  - TTE or MUGA pre 1st dose & every three months thereafter

Verma, 2012
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf

Metastatic Breast Cancer
Triple Negative

Triple Negative MBC

Who's at risk?

- History of TNBC
- Residual disease following neoadjuvant chemotherapy[1]
- BRCA1 > BRCA2[2]
  - NCCN recommends women ≤60 with TNBC be screened

1. Liedtke et al., 2008
2. NCCN Guidelines for Genetic/ Familial High Risk Assessment: Breast and Ovarian, 2016

Triple Negative MBC

- Treatment considerations
  - Disease symptoms
  - Visceral crisis
  - Patient goals
- No clear guidelines, research emerging
  - PDL1 inhibitors
  - Platinums
  - eribulin

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Triple Negative MBC pembrolizumab

- Anti PD-1
  - Inhibits cell death and allows cancer cell invasion
  - pembrolizumab blocks the PD-L1 and PD-L2 receptors
  - Approved in melanoma, metastatic NSCLCa
  - Not yet approved in TNMBC
- Phase 1b trial: Keynote-012, N=27
  - TNBC expressing PD-L1
  - Pretreated patients
  - ORR 18.5%; 1 CR, 4 PR, 7 SD
- Phase 2 currently enrolling
  - TNBC
  - Stratification between pretreated and de novo stage IV disease

…More to come…

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Buisseret et al., 2015

Nursing Considerations pembrolizumab

Reference package insert for dose modifications and management of the following:

- Inflammatory response
  - Think “–itis” (nephritis, pneumonitis, colitis, hepatitis, etc)
- Fatigue
- Nausea
- Anorexia
- Infusion related reaction

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

Triple Negative MBC Platinums

- TNT, phase III
  - First line
  - TN or BRCA 1/2 + (any ER/ PR/ Her2 status)
  - Q3 week docetaxel vs. q 3 week carboplatin
  - Only benefit of platinums seen in the BRCA population
    - ORR 68.8% vs 33%
    - PFS 6.8 mo vs 4.8 mo
  - Carboplatin arm
    - BRCA status drove response
    - + PFS 6.8 mo vs. -3.1 mo
  - Mechanism of action suspected to be secondary to difficult DNA repair in BRCA mutated lesions after exposure to platinums

Tutt et al., 2015.

Triple Negative MBC
eribulin

Study 301, phase III

- eribulin superior to capecitabine in TNBC
  - No superiority in non-TN patients
  - Improvement in OS 14.4% vs. 9.4%
  - Consider *for first line treatment* of TNMBC

Kaufman et al., 2015.

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Skeletal Related Events (SRE)

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Skeletal Related Events

- May occur in up to 64% of individuals with bone metastasis who are untreated
- Prevention
  - zoledronic acid - 4mg IV
  - denosumab- 120mg SQ

Costa et al., 2008.

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Skeletal Related Events zoledronic acid (ZA)

- OPTIMIZE-2
  - Randomized ZA
    - Monthly vs. quarterly following 12 monthly treatments
    - Powered for non-inferiority
    - Results: quarterly non-inferior to monthly
      - 22% vs. 23.3% SRE rate
      - Fewer AEs and no cases of ONJ
      - Similar rates of bone turnover

Hortobagyi et al., 2014

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Audience Response Question

Are you ready to answer?

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Skeletal Related Events

58 y/o female with metastatic breast cancer recently stubbed her R toe and developed acute, intractable R hip pain. She has been on zolendronate for 18 months along with an aromatase inhibitor. What disease related diagnosis should be in your differential based on her current treatment?

1. Fracture secondary to disease progression
2. Atypical femur fracture
3. Fracture secondary to aromatase inhibitor induced osteoporosis
4. All of the above

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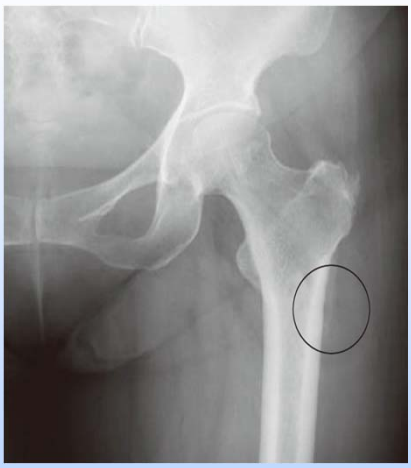
Skeletal Related Events
ZA Nursing Considerations

- Osteonecrosis of the Jaw (ONJ)
  - Fewer incidents with q3mo vs. q4 week[1]
  - Those at risk
    - Poor dentition
    - Recent or upcoming extractions/ implants
  - Avoid invasive dental procedures
  - Pretreatment dental exam
- Atypical femur fractures
  - Uncommon, but real risk- approx 1.2% [2]
  - May present with prodromal thigh pain



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1. Hortobagyi et al., 2014
2. Puhaindran et al., 2011

Skeletal Related Events
ZA Nursing Considerations

- Renal impairment
  - Renally excreted
  - Pretreatment creatinine
    - Adjust dose for CC <60
    - Do not administer with CC <30
  - Hydration day of and day following treatment
- Arthralgia
  - Most common after first treatment
  - Premedicate with OTC analgesics and prn
- Encourage Ca & Vit D Supplementation

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Skeletal Related Events
denosumab

- RANK ligand inhibitor given every 4 weeks
  - Intercepts tumor secretion of RANKL
  - Reduces osteoclast formation
- Randomized controlled placebo trial
  - Measured uNTx/Cr to evaluate bone turnover
  - Goal to reduce uNTx/Cr by 90%
    - 120mg suggested to suppress 95% of individuals 90%

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Lipton et al., 2007

Skeletal Related Events
zoledronic acid vs. denosumab

- Randomized, double-blind, double-dummy active controlled study
- 4mg IV zolendronate vs. 120mg SQ denosumab
- Denosumab delayed for SRE by 23% over zoledronic acid
- Greater degree of uNTx/Cr suppression with denosumab (80% vs. 63%)
- OS, disease progression and AE rates were similar

MAYO CLINIC

Stopeck et al., 2010

Skeletal Related Events denosumab Nursing Considerations

- Hypocalcemia
  - Ca and Vit D supplementation suggested
  - Evaluate calcium before each injection
  - May result in treatment delays
- Osteonecrosis of the Jaw
  - ~2.0% incidence
  - Risk factors
  - Pretreatment dental exam
  - Avoid invasive dental procedures
- $$$
  - Ongoing studies
  - Dynamic findings

MAYO CLINIC

Stopeck et al., 2010

Take Home Points

- Data is constantly emerging.
- Nurses are vital in the success of our patients.
- **Anticipatory Guidance. Anticipatory Guidance. Anticipatory Guidance.**

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