Chemorx Induced Anemia/Fe/ESAs, and Bone Health/Mets, and Biosimilars...?Seriously!

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Pennsylvania Hospital
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OUTLINE

- Chemorx Induced Anemia
  - ESAs and IV Fe
- Bone
  - Healthy and Metastatic
- Biosimilars
  - So what are they?
Brief Workup to Determine the Cause of Anemia

- Reticulocyte count
- Creatinine
- Iron studies – Fe, TIBC, Ferritin
- B12
- Folate
# Iron or Vitamin B12 Deficiency in Anemic Cancer Patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Number</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
<th>Laboratory reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>256</td>
<td>10.1 (1.0)</td>
<td>10.3 (6.8-12.6)</td>
<td>12-15 (women) 14-17 (men)</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>261</td>
<td>455.0 (480.0)</td>
<td>299.0 (3.0-2,761.0)</td>
<td>10-120 (women) 20-50 (men)</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td>259</td>
<td>21 (14)</td>
<td>18 (3-87)</td>
<td>15-50 (women) 20-50 (men)</td>
</tr>
<tr>
<td>Iron, µg/dL</td>
<td>261</td>
<td>61 (40)</td>
<td>51 (9-251)</td>
<td>30-160 (women) 45-160 (men)</td>
</tr>
<tr>
<td>Transferrin, mg/dL</td>
<td>261</td>
<td>228 (50)</td>
<td>223 (79-433)</td>
<td>200-400</td>
</tr>
<tr>
<td>Reticulocyte hemoglobin content, pg</td>
<td>255</td>
<td>34.3 (4.1)</td>
<td>33.9 (25.1-44.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypochromic red blood cells, %</td>
<td>255</td>
<td>7.2 (8.3)</td>
<td>4.7 (0-53.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Red blood cell distribution, %</td>
<td>218</td>
<td>18.0 (2.7)</td>
<td>17.7 (12.5-26.8)</td>
<td>11.5-14.5</td>
</tr>
<tr>
<td>Reticulocytes, % red blood cells</td>
<td>251</td>
<td>2.9 (1.6)</td>
<td>2.8 (0.2-12.9)</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td>Red blood cell folate, ng/mL</td>
<td>216</td>
<td>1,182.9 (1,706.7)</td>
<td>919.5 (302.0-23,718)</td>
<td>93-641</td>
</tr>
<tr>
<td>Serum B12, pg/mL</td>
<td>226</td>
<td>1,603.4 (2,312.2)</td>
<td>648.0 (107-15,005)</td>
<td>220-960</td>
</tr>
<tr>
<td>Urea (blood urea nitrogen), mg/dL</td>
<td>261</td>
<td>15.9 (7.1)</td>
<td>15.0 (3.0-66.0)</td>
<td>9-24</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>261</td>
<td>0.8 (0.3)</td>
<td>0.7 (0.3-1.9)</td>
<td>0.5-1 (women) 0.6-1.4 (men)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>261</td>
<td>3.6 (0.4)</td>
<td>3.6 (2.2-4.6)</td>
<td>3.7-4.9</td>
</tr>
</tbody>
</table>

SD = standard deviation; N/A = not applicable

Ferritin in CIA


n = 261
ACD, Iron Availability, & Hepcidin

FE RESTRICTED ERYTHROPOIESIS…

Fe Deficiency – out of Fe (EPO Sky High!)

ACD – Plenty of Fe, but Hepcidin causes Fe stores lock up in BM (EPO up, but not enough)
ESA and Mortality in Cancer Patients

60 Trials
n = 15,323
HR 1.06 (0.97-1.15)
So, What was all the Hub Bub about ESAs and Tumor Progression and Survival?

Only 8 Trials raised this issue.

Only 4 of them were in CIA

Patients had higher Target HGBs, but did they hit them or not?

Patients had ESA doses continued and even increased, but did they respond or not?
Of the 60 Trials, 8 Largely Responsible for the Safety Signal

Table 3. Summary of 8 Trials That Individually Demonstrate Increased Mortality and/or Tumor Progression Among Patients Treated With ESA

<table>
<thead>
<tr>
<th>Source</th>
<th>Cancer Type</th>
<th>Concomitant Treatment</th>
<th>No. of Patients Randomized</th>
<th>ESA Treatment</th>
<th>Hemoglobin Stopping Value, g/dL</th>
<th>Adverse Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henke et al.</td>
<td>Advanced (stage III, IV) head and neck cancer</td>
<td>Radiotherapy</td>
<td>351</td>
<td>Epoetin beta (300 IU/kg x 3/wk)</td>
<td>≥14 (women) ≥15 (men)</td>
<td>Locoregional progression (HR, 1.68; P = .007); HR for death, 1.39; P = .02</td>
</tr>
<tr>
<td>Hedenumus et al.</td>
<td>Lympho-proliferative cancers</td>
<td>Chemotherapy</td>
<td>349</td>
<td>Darbepoetin alfa (2.25 μg/kg/wk)</td>
<td>≥14 (women) ≥15 (men)</td>
<td>Shortened overall survival; HR for death, 1.37; P = .04</td>
</tr>
<tr>
<td>Layland-Jones et al.</td>
<td>Metastatic breast cancer</td>
<td>Chemotherapy</td>
<td>939</td>
<td>Epoetin alfa (40 000 U/wk)</td>
<td>&gt;14</td>
<td>Survival at 12 mo ESA vs placebo, 70% vs 76% (P = .01)</td>
</tr>
<tr>
<td>Wright et al.</td>
<td>Metastatic non-small cell lung cancer</td>
<td>Chemotherapy</td>
<td>70</td>
<td>Epoetin alfa (40 000 U/wk)</td>
<td>&gt;14</td>
<td>Overall survival vs placebo, 63 vs 129 d; HR for death, 1.84; P = .04</td>
</tr>
<tr>
<td>Overgaard et al.</td>
<td>Locally advanced head and neck cancer</td>
<td>Radiotherapy</td>
<td>522</td>
<td>Darbepoetin alfa (150 μg/wk)</td>
<td>&gt;15.5</td>
<td>Increased risk in local-regional failure (RR, 1.44; P = .03); trend toward shorter survival (RR, 1.28; P = .08)</td>
</tr>
<tr>
<td>Glaapy et al.</td>
<td>Nonmyeloid cancers in patients not receiving chemotherapy or myelosuppressive radiation therapy</td>
<td>None</td>
<td>985</td>
<td>Darbepoetin alfa (6.75 μg/kg/wk)</td>
<td>≥13</td>
<td>Shorter overall survival; HR for death, 1.30; P = .008</td>
</tr>
<tr>
<td>PREPARE, 2008</td>
<td>Breast cancer</td>
<td>Chemotherapy</td>
<td>733</td>
<td>Darbepoetin alfa (4.5 μg/kg/2 wk)</td>
<td>≥13</td>
<td>Shortened survival overall (14% death ESA vs 9% death placebo); faster tumor growth</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Cervix carcinoma</td>
<td>Chemo-radiotherapy</td>
<td>113</td>
<td>Darbepoetin alfa (40 000 U/wk)</td>
<td>&gt;14</td>
<td>Shortened survival overall and faster tumor growth (42% death and free of cancer growth ESA vs 34% placebo)</td>
</tr>
</tbody>
</table>

Abbreviations: ESA, erythropoiesis-stimulating agent; HR, hazard ratio; RR, relative risk.
* These trials were recently identified by 2 US Food and Drug Administration safety advisories. 25, 52

Bennett, CL et al. JAMA. 2008; 299: 914-924
Pooled Analysis RCTs, Darbepoetin Alfa in CIA

n = 2,122; 7 RCTs

Ludwig et al. Pooled Analysis of Individual Patient-Level Data From All Randomized, Double-Blind, Placebo-Controlled Trials of Darbepoetin Alfa in the Treatment of Patients With Chemotherapy-Induced Anemia. JCO 2009
Negative Outcome was in…
ESA or PBO, Non Responder, Transfusion

Impact of Transfusions on Adverse Outcomes

- Death with follow-up (DA)*: HR 1.28 (1.03 to 1.60)
- Death with follow-up (Placebo): HR 1.60 (1.32 to 1.95)
- PFS with follow-up (DA)*: HR 1.43 (1.20 to 1.70)
- PFS with follow-up (Placebo): HR 1.49 (1.26 to 1.76)
- Embolism/thrombosis (DA)*: HR 1.90 (1.14 to 3.15)
- Embolism/thrombosis (Placebo): HR 0.93 (0.44 to 1.96)

n = 2,122; 7 RCTs

Ludwig et al. Pooled Analysis of Individual Patient-Level Data From All Randomized, Double-Blind, Placebo-Controlled Trials of Darbepoetin Alfa in the Treatment of Patients With Chemotherapy-Induced Anemia. JCO 2009
Consistent Safety Signal Of Venous Thromboembolism (VTE) Of About 1.5

HR 1.48 (1.28-1.72)

Glaspy, Br J Cancer 2010
Epoetin Alfa Licensing Trial, 1993

- EPO 150 U/Kg SQ TIW vs PBO  
  \( n = 289 \)

- Hgb, BTx, and QOL significantly better in EPO arm than in PBO arm

Abels  *Eur J Cancer* 1993
Darbepoetin Alfa Licensing Trial, 2002

DBO 2.25 µg/kg SQ q7d vs PBO
BTx, Hgb, QOL
Significantly Better in DBO arm

Vansteenkiste JNCI 2002
ESAs and IV Fe

If ACD, in part, due to relative EPO insufficiency, then giving ESA could augment Hgb response.

But, if ACD is combination of inadequate EPO AND Fe-restricted erythropoiesis from inflammatory cytokines and Hepcidin, then

Could giving BOTH ESA and IV Fe give an even better response?
IV Iron in Nephrology: DRIVE I Study

- ESA in CRF on hemodialysis
- Hgb levels increased & at a greater rate in IV iron group, independent of baseline ferritin or TSAT
- Significant reductions in ESA usage

Coyne J Am Soc Nephrol 2007
IV Iron and rEPO in Patients with CIA: Mean Change in Hgb

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change in Hgb, g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No iron</td>
<td>0.9</td>
</tr>
<tr>
<td>Oral iron</td>
<td>1.5</td>
</tr>
<tr>
<td>Bolus</td>
<td>2.5&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TDI</td>
<td>2.4&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ITT population

- Ferritin<675
- TSAT<19%

Overall changes from baseline, \( P<0.0001 \). Overall difference between groups, \( P<0.0001 \).

<sup>a</sup>Differs from no iron group, \( P<0.05 \).<sup>b</sup>Diffs from oral iron group, \( P<0.05 \).

Epoetin & IV Ferric Gluconate in CIA

Ferritin $\geq 100$
or TSAT $\geq 15$

No Fe
PO Fe
q7d 125mg IV

n = 129

Henry Oncologist 2007
Darbepoetin 300 or 500 µg q3w ± IV LMW Fe Dextran

Cumulative Percent

Study Week

Time to Hematopoietic Response
K-M Median Weeks (95% CL)

No IV Iron
IV Iron

12 (10, 15) 8 (7, 9)

Hematopoietic Response

DBO 300 + IV Fe 79%
DBO 500 – IV Fe 68%

Auerbach AJH 2010
STUDY SCHEMA

DBO 100μg or EPO 40K units

Fixed Dose ESA

Fixed Dose ESA Responders

Group A
(ESA + Iron sucrose IV)

Group B
(ESA)

Fixed Dose ESA Non-Responders

Group C
(ESA + Iron sucrose IV)

Group D
(ESA)

Wk -8 -6 -3 0 Wk 0 3 6 9 (12)

Stage 1 Study Visits (8 week ESA)

Stage 2 Study Visits (12 week ESA + Iron)

(Randomization)

Bellet, ASCO 2007

*Erythropoiesis stimulating agent (ESA) (darbepoetin or epoetin)
## Maximum Improvement in Hgb Levels over Baseline after IV Iron Sucrose Compared to No Iron in ESA Treated Patients

### Results

<table>
<thead>
<tr>
<th>Maximum Hgb Change</th>
<th>Iron Sucrose plus ESA</th>
<th>ESA only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (R)</td>
<td>Group C (NR)</td>
</tr>
<tr>
<td><strong>Intent to Treat Population</strong></td>
<td>N=59</td>
<td>N=40</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.6 (1.6)</td>
<td>2.5 (1.9)</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Minimum – Maximum</td>
<td>0 – 7</td>
<td>0 – 7</td>
</tr>
<tr>
<td>p-value (A+C) vs. (B+D)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>p-value (A) vs. (B)</td>
<td>0.004*</td>
<td></td>
</tr>
<tr>
<td>p-value (C) vs. (D)</td>
<td></td>
<td>0.027</td>
</tr>
</tbody>
</table>

### Evaluable Population

<table>
<thead>
<tr>
<th>Maximum Hgb Change</th>
<th>N=41</th>
<th>N=31</th>
<th>N=53</th>
<th>N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>2.9 (1.7)</td>
<td>2.6 (2.0)</td>
<td>2.1 (1.4)</td>
<td>1.6 (2.0)</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Minimum – Maximum</td>
<td>0 – 7</td>
<td>0 – 7</td>
<td>0 – 6</td>
<td>0 – 7</td>
</tr>
<tr>
<td>p-value (A+C) vs. (B+D)</td>
<td>0.0021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value (A) vs. (B)</td>
<td></td>
<td>0.0081*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value (C) vs. (D)</td>
<td></td>
<td></td>
<td>0.0819</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** SD=Standard Deviation; R=responders and NR=non-responders based on response to ESA during Stage 1
All p values are from the ANCOVA analysis
* Primary Endpoint

Bellet, ASCO 2007
Proportion of Patients Achieving Hgb Response or Requiring Transfusions on Hepcidin Tertiles: MC04CC Trial

<table>
<thead>
<tr>
<th></th>
<th>DA + placebo (n=163)</th>
<th>DA + oral iron (n=163)</th>
<th>DA + IV iron (pts receiving &lt;4 doses IV iron) (n=71)</th>
<th>DA + IV iron (pts receiving 4 or 5 doses IV iron) (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of patients achieving an erythropoietic (Hgb) response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>106/163 (65%)</td>
<td>109/163 (67%)</td>
<td>40/71 (56%)</td>
<td>74/92 (80%)</td>
</tr>
<tr>
<td>Hepcidin 1st tertile (≤20.2 ng/mL)</td>
<td>30/47 (64%)</td>
<td>26/41 (63%)</td>
<td>12/20 (60%)</td>
<td>24/26 (92%)</td>
</tr>
<tr>
<td>Hepcidin 2nd tertile (&gt;20.2-64.3 ng/mL)</td>
<td>36/53 (68%)</td>
<td>32/53 (60%)</td>
<td>6/11 (55%)</td>
<td>20/21 (95%)</td>
</tr>
<tr>
<td>Hepcidin 3rd tertile (&gt;64.3 ng/mL)</td>
<td>23/36 (64%)</td>
<td>29/37 (78%)</td>
<td>14/24 (58%)</td>
<td>25/36 (69%)</td>
</tr>
<tr>
<td>Hepcidin missing</td>
<td>17/27 (63%)</td>
<td>22/32 (69%)</td>
<td>8/16 (50%)</td>
<td>5/9 (56%)</td>
</tr>
<tr>
<td><strong>Proportion of patients who required RBC transfusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>22/163 (13%)</td>
<td>21/163 (13%)</td>
<td>12/71 (17%)</td>
<td>8/92 (9%)</td>
</tr>
<tr>
<td>Hepcidin 1st tertile</td>
<td>6/47 (13%)</td>
<td>4/41 (10%)</td>
<td>2/20 (10%)</td>
<td>0/26 (0%)</td>
</tr>
<tr>
<td>Hepcidin 2nd tertile</td>
<td>8/53 (15%)</td>
<td>9/53 (17%)</td>
<td>2/11 (18%)</td>
<td>0/21 (0%)</td>
</tr>
<tr>
<td>Hepcidin 3rd tertile</td>
<td>6/36 (17%)</td>
<td>5/37 (14%)</td>
<td>4/24 (17%)</td>
<td>6/35 (17%)</td>
</tr>
<tr>
<td>Hepcidin missing</td>
<td>2/27 (7%)</td>
<td>3/32 (9%)</td>
<td>4/16 (25%)</td>
<td>2/9 (22%)</td>
</tr>
</tbody>
</table>
• FDA MedWatch reports (2001-2003) show HMWID was associated with a 3.4-fold increase in odds of life-threatening AEs

• This analysis likely underestimates AEs with HMWID and overestimates AEs with LMWID (all AEs reported by generic name only where attributed to LMWID)

IV Fe Only in CIA

Kim: 75 Cx Ca patients on ChemoXRT
  • 200 mg IV Iron Sucrose Weekly or none
  • BTx: 40% vs 64%

Dangsuwan: 44 GYN Ca patients on Chemorx
  • After 1st BTx, 200 mg IV Iron Sucrose or PO Iron
  • Subsequent BTx: 22.7% vs 63.6%

Kim Gyn Oncol 2007; Dangsuwan Gyn Oncol 2009
NCCN Guidelines for IV Fe in CIA

Iron Studies: Iron Panel (serum iron, total iron binding capacity, serum ferritin)

- Functional Iron Deficiency (ferritin < 800 mg/mL and transferrin saturation < 20%)
  - Consider IV iron supplementation with erythropoietic therapy

- No Iron Deficiency (ferritin > 800 mg/mL or transferrin saturation > 20%)
  - IV or PO iron supplementation is not needed
SUMMARY

• Anemia is common in cancer patients

• R/O other causes of anemia

• ESA safety profile quite good when used on label (CIA, Hb < 10)…BUT avoid continuing ESA in CIA if insufficient response after 6-8 weeks

• Available evidence suggests that IV FE can limit ESA-induced Fe restricted erythropoiesis, even in Fe replete patient, and improve ESA response
Minimum Vitamin D Levels

- 25(OH) vitamin D levels considered to be adequate
  - General population: 20 ng/mL (50 nmol/L)[1]
  - Older men/women: ≥ 30 ng/mL (75 nmol/L)[2]
  - Patients with cancer: ≥ 30 ng/mL (75 nmol/L)[2,3]

# Recommendations for Vitamin D Supplementation in Patients With Cancer

<table>
<thead>
<tr>
<th>serum 25(OH)D</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 ng/mL (deficiency)</td>
<td>- Vitamin D2 or D3 50,000 IU qw for 8 wks, then as needed (eg, q2w) for maintenance</td>
</tr>
<tr>
<td>20-30 ng/mL (insufficiency)</td>
<td>- Vitamin D2 or D3 800-1000 IU/day</td>
</tr>
<tr>
<td>≥ 30 ng/mL</td>
<td>- Continue current practice</td>
</tr>
</tbody>
</table>

Conclusions: Vitamin D and Calcium Supplementation in Patients With Cancer

25(OH) vitamin D and calcium insufficiency/deficiency common among patients with cancer
  • Due to both cancer and its treatment
  • Adverse consequences of deficiency include loss of BMD and risk of fracture
  • Supplementation recommended to bring levels within target goals
    • 25(OH) vitamin D goal: ≥ 30 ng/mL (75 nmol/L)
    • Calcium goal: 1000-1200 mg/day dietary calcium

Clinicaloptions.com
Treatments for Cancer Can Cause Osteopenia and Osteoporosis

- Bilateral oophorectomy
- Bilateral orchiectomy
- Chemotherapy-induced ovarian failure
- Aromatase inhibitors
- GnRH agonists
- Glucocorticoids

Hypogonadism → Elevated bone turnover → Bone loss → Diminished bone quality

Clinicaloptions.com
Case

- 64-yr-old woman with breast cancer
  - T2, 4+ nodes, ER+, PgR+, HER2/neu negative
- Height: 5'4"; weight: 132 lbs
- No personal history of fracture, current use of tobacco, alcohol, rheumatoid arthritis
- Maternal history of hip fracture
- Limited physical exercise
- 25(OH)D level: 20 ng/mL (50 nmol/L)
- She is treated with adjuvant chemotherapy followed by an aromatase inhibitor
Bone Loss With Cancer Therapies

Naturally Occurring Bone Loss

- Normal Men[^1] 0.5%
- Postmenopausal Women[^1] 1.0%
- Menopausal Women[^1] 2.0%
- Al Therapy in Postmenopausal Women[^2] 2.6%
- ADT[^3][^3] 4.6%
- Al Therapy + GnRH Agonist in Premenopausal Women[^4] 7.0%
- Premature Menopause Secondary to Chemotherapy[^5] 7.7%

Clinicaloptions.com

Expert Insight: 5 Breast Cancer Experts’ Choice of Therapy for This Patient

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Clinicaloptions.com

Online Expert Insight tool available at:
http://www.clinicaloptions.com/Oncology/Resources/Tool%20Download.aspx

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**Expert Guidance on Bone-Targeted Therapy for Patients With Breast Cancer**

<table>
<thead>
<tr>
<th>Expert</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert 1</td>
<td>Alendronate 70 mg once every week</td>
</tr>
<tr>
<td>Expert 2</td>
<td>Zoledronic acid 4 mg once every 6 months</td>
</tr>
<tr>
<td>Expert 3</td>
<td>Alendronate 70 mg once every week</td>
</tr>
<tr>
<td>Expert 4</td>
<td>Alendronate 70 mg once every week</td>
</tr>
<tr>
<td>Expert 5</td>
<td>Alendronate 70 mg once every week</td>
</tr>
</tbody>
</table>
### Practical Guidance for Prevention of CTIBL

- **T-score ≥ -2.0, no risk factors**
  - Exercise; calcium and vitamin D supplements
  - Monitor risk status and BMD at 1 yr*

- **T-score < -2.0**
  - Bone-targeted therapy; exercise; calcium and vitamin D supplements
  - Monitor BMD every 1-2 yrs for oral BPs; otherwise on an individual basis

#### Any 2 of the following risk factors:
- T-score < -1.5
- Older than 65 yrs of age
- Low BMI (< 20)
- Family history of hip fracture
- Personal history of fragility fracture after 50 yrs of age
- Oral corticosteroid use of > 6 mos
- Smoking (current and/or history of)

*Consider bone-targeted therapy if annual decrease in BMD ≥ 10% or ≥ 5% in pts who were osteopenic at baseline. Use lowest T-score from 3 sites.

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Clinicaloptions.com

Back to Our Case

- Patient given alendronate 70 mg/wk
- 3 yrs later while on AI therapy, she develops bone metastases
Expert Insight: 5 Breast Cancer Experts’ Choice of Therapy for This Patient

Expert Guidance on Bone-Targeted Therapy for Patients With Breast Cancer

**Patient Summary**
- Patient has bone metastases?
  - Yes
- Creatinine clearance < 60 mL/min?
  - No

**Selected Therapy**
- Bone-targeted therapy?
  - Unsure

**Recommendations**
- **Expert 1**: Zoledronic acid 4 mg once every 4 weeks
- **Expert 2**: Zoledronic acid 4 mg once every 4 weeks
- **Expert 3**: Zoledronic acid 4 mg once every 4 weeks
- **Expert 4**: Denosumab 120 mg once every 4 weeks
- **Expert 5**: Denosumab 120 mg once every 4 weeks

Clinicaloptions.com

Online Expert Insight tool available at:
http://www.clinicaloptions.com/Oncology/Resources/Tool%20Download.aspx
Patients With Bone Lesions Are at High Risk for Skeletal Complications

- Pathologic fracture
- Radiation therapy
- Surgical intervention
- Spinal cord compression

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Placebo Arms of Large Randomized Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast[1] 24 mos</td>
<td>52</td>
</tr>
<tr>
<td>Prostate[2] 24 mos</td>
<td>33</td>
</tr>
<tr>
<td>Multiple myeloma[3,4] 21 mos</td>
<td>37</td>
</tr>
<tr>
<td>NSCLC + other solid tumors[5] 21 mos</td>
<td>34</td>
</tr>
</tbody>
</table>

- 21-mo data except for surgical intervention and spinal cord compression, for which only 9-mo data are available.

Zoledronic Acid Significantly Delays Time to First SRE Compared With Placebo

Proportion of Patients With Bone Metastases Without an SRE

$P = .004$

Zoledronic acid 4 mg
Placebo

Time to First On-Study SRE

HR: 0.82 (95% CI: 0.71-0.95; P < .001 noninferiority; P = .01 superiority*)

Proportion of Subjects Without SRE

Patients at Risk, n
- Zoledronic acid: 1020, 829, 676, 584, 498, 427, 296, 191, 94, 29

*Adjusted for multiplicity.
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zoledronic Acid (n = 1013)</th>
<th>Denosumab (n = 1020)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>97.2</td>
<td>95.8</td>
</tr>
<tr>
<td>Serious</td>
<td>46.5</td>
<td>44.4</td>
</tr>
<tr>
<td>Acute phase reactions (first 3 days)</td>
<td>27.3</td>
<td>10.4</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>8.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Serious</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>ONJ*</td>
<td>1.4</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*P = .39

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Skeletal Complication Risk: Incremental Benefits in Breast Cancer

No bisphosphonate
64% risk at 2 yrs

Pamidronate
~ 20% risk reduction

Zoledronic acid
Additional ~ 20% risk reduction

Denosumab
Additional 18% risk reduction

64% 51% 34% 27%

Breast Cancer Recurrence: Postmenopausal Women

All Distant Recurrence

11036 women 1564 events

Bisphosphonates

No Bisphosphonates

10-yr gain 3.5% (SE: 1.2)

Log-rank 2P = .0003

18% Relative Reduction

13.9%

11.3%

21.9%

18.4%

Bone Recurrence

11036 women 508 events

10-yr gain 2.9% (SE: 0.8)

Log-rank 2P < .00001

34% Relative Reduction

5.1%

3.2%

5.9%

Bone Recurrence Outside Bone

11036 women 1056 events

10-yr gain 0.9% (SE: 1.0)

Log-rank 2P = .24

8% Relative Reduction

9.2%

8.4%

14.3%

13.3%

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Biosimilars 101

- Biologics are therapeutic agents manufactured using biologic pathways in cellular systems
  - Examples: monoclonal antibodies, G-CSF
- Complex manufacturing process, so biologics are not easily produced by others
- A generic chemical medication has an identical structure to the original

Hirsch BR, Lyman GH. JNCCN 2013. 1291-1296.
Acetylsalicylic acid
Small molecule

21 atoms

IgG1 antibody
Biologic medicine

> 20,000 atoms
Even if a biosimilar uses the same human gene as its originator, it will differ in other parts of the process. **Different process = different product**
Biosimilars 101

- Biosimilars must have analytical, non-clinical and clinical data similar to the Original Biologic in structure, safety, and efficacy.

- Biosimilars are not exact copies of the Original Biologic so are therefore not the same as generic drugs.

- Minor differences with the active ingredient are expected and permitted so long as any such differences are demonstrated not to be clinically meaningful.

Hirsch BR, Lyman GH. JNCCN 2013. 1291-1296.
Biosimilars 101

• As an alternative to a new Biologic (Brand new medicine), Biosimilars provide potential cost savings and improved availability of an established drug

• However, there are still regulatory and legal concerns that are limiting their widespread use in the United States

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Drug Makes Corn Grow Faster
XXX...YYY
New Drug could be...

* New Biologic
* AAA...BBB
* Long Dev Time
* $$$$$$

* New Biosimilar
* *XXX...YYY*
* Short Dev Time
* $$
Regulatory Concerns for Biosimilars

• What “comparability” is expected to be demonstrated and what evidence is necessary for approval?

• What is the potential for differing immunogenicity?
  • Monitor patients receiving given agent after approval for unanticipated AEs (pharmacovigilence)
  • Example….Epoetin and PRCA

Hirsch BR, Lyman GH. JNCCN 2013. 1291-1296.
Importance of Biosimilars in Reducing Costs

- As of 2010, Biologics represented the top 3 agents with the highest revenues in outpatient oncology practices:
  - Bevacizumab (Avastin), rituximab (Rituxan), trastuzumab (Herceptin)
- This trend is likely to continue, as Biologics represent the majority of oncology products under development
- By comparison, Biosimilars are likely to be priced at 20-40% discount compared to biologics

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Regulatory Framework for Biosimilars in US

The regulatory framework for Biosimilars is slowly making progress:

- Biologics Price Competition and Innovation Act (2010) defined biosimilarity
- The FDA is reviewing agents on case-by-case basis, so difficult for manufacturers, because concerned about regulatory approval
- As of April 2013, no submissions made for regulatory approval in US of a Biosimilar

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Regulatory Framework for Biosimilars in Europe

• By comparison to the US, Europe has a more defined pathway for approval of biosimilar agents:
  • The first Biosimilar was approved in 2006

• However, uptake and use of Biosimilars is still limited:
  • Uncertainty about the true comparability
  • Lack of large-scale approval trials
  • Original agents cut prices to remain competitive

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Test Case: Tbo-Filgrastim

- Tbo-filgrastim is a biosimilar form of G-CSF
  - It is available in Europe under the name Tevagrestim
  - It has been recently released in the US under the name Granix (as a New Biologic!!!)
- In 2012, an industry-funded study in Europe found a 26-34% cost savings in Tbo-filgrastim over filgrastim
- Biologic or Biosimilar…a Biosimilar must show comparative manufacture, efficacy, and safety

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Future for Biosimilars

• Biosimilars continue to face an uphill battle in the US due to concerns about regulatory approval process

• Biosimilars offer great potential for reducing health care costs, but not clear if enough motivation for widespread development and use of these agents

Hirsch BR, Lyman GH. JNCCN 2013. 1291-1296.
Acknowledgements

- Jessica Langholtz, MS2, Jefferson University School of Medicine