Targeting Supportive Care:

Emesis
Anemia
Myelosuppression

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Texas Oncology
US Oncology - Houston TX

John Hersey, NY Times Science Times 11-9-10
SUMMARY EMESIS

- “Emetogenic profile”: female, young, thin, emesis with pregnancy, no or low alcohol
- Anthracycline + cyclophosphamide (AC) is HIGHLY emetogenic (AC = HEC)
  - need triple therapy with aprepitant
- “Emesis risk period” = 5 days, 1-5
- 3 classes of major antiemetics:
  - 5HT3 receptor antagonists;
  - Steroids;
  - NK-1 inhibitors
EMESIS cont’d

• Palonosetron’s binding characteristics & chemistry make it superior to 1st generation 5HT3RA

• Dexamethasone is critical; 12 mg day 1; 4-8 mg days 2-4 single dose

• Most potent antiemetic combination = 1 from each class: palonosetron, aprepitant, dexamethasone

• Olanzapine, not FDA approved, is effective for breakthrough & refractory N/V

• GERD rx CRITICAL
ANEMIA

- ESAs contraindicated if curative intent
- New data refute ESA’s negative effects on tumor progression and survival but confirm increased incidence of thrombosis even when used to maintain Hgb \( \leq 12 \) g
- Inflammatory cytokines cause anemia of cancer, impair iron metabolism
- Treat correctable causes, iron deficiency
- Transfuse if symptomatic
MYELOSUPPRESSION & MGF’s (aka CSF’s)

• Cycle 1 is highest risk for FN
• Use MGFs for regimens with 20%+ risk FN or high risk pts (older, organ dysfunction, wounds, etc)
• Give MGFs day AFTER if possible but limited data show SAME day ok
• Prophylactic antibiotics decrease FN by 50%; quinolones by 67%; no serious toxicity
• Tbo-filgrastim is approved biosimilar
Emesis: You have ONE CHANCE to make a GOOD 1st IMPRESSION

Pavlov & one of his dogs: “operant conditioning”

ANTICIPATION
Anticipatory N/V
What are the goals of emesis rx?

• “Zero tolerance policy”: Prevent it
  ➢ Use most effective drugs, lowest dose
  ➢ KNOW side effects of drugs (constipat’n!)

• Treat for ACUTE & DELAYED emesis
  ➢ Highly emetogenic: at least 5 days
  ➢ Moderately emetogenic: 3-5 days

• IV & Oral drugs equally effective

• “Personalize” (“precision”) therapy by:
  ➢ Treatment factors
  ➢ Patient “host” factors

• Be alert to non-chemo causes: “LEGEND”

www.nccn.com
What are the NON-CHEMO causes of N/V? L-E-G-E-N-D-S

- **LYTES, Metabolic** (Ca$$^{++}$$, BUN)
- **EAR:** vestibular
- **GUT:** GERD; obstruction, ileus 2º drugs, diabetes
- **EMOTIONAL:** anticipatory, anxiety
- **NEURO:** Brain, LMD mets
- **DRUGS:** Opioids, Antibiotics
- **SEX:** Estradiol

www.nccn.org
What is the “profile” of the pt at highest risk for CINV?

- Young, slender
- Non-smoker
- Non-drinker
- Emesis with pregnancy
- Motion sickness
- GERD
- DM-gastroparesis
Does the time of onset of emesis inform us of pathophysiology & patho-anatomy? Yes

Anticipatory*: day –7 to 1; cortex; conditioned

Acute: 0-24 h Serotonin; gut-EC cell

Delayed 16-120 h Sub P; brain stem

Breakthru within 5 d of initial; Dopamine, SubP, Muscarinic, Histamine

Martin M. *Oncology. 1996;53(suppl 1):26
*Roscoe JS. *Support Care Cancer 2011; 19:1533
So treating (preventing) emesis is no different than treating HER2 positive breast cancer...fit the right drug to block the receptor!
Where are the receptors for these neurotransmitters located?

Brain stem (medulla):
- 5-HT3R (serotonin)
- NK-1R (Substance P)
- D2R (dopamine)

Gut (Enterochromafin cells “EC”):
- 5-HT3R

Slusher B. Clin Adv Hem Oncol 2013 (Suppl1) 11:3
How is emesis graded? By % pts w/ emesis w/o premeds. What rx are Highly Emetogenic “HEC”? AC

<table>
<thead>
<tr>
<th>Grade</th>
<th>Drugs</th>
<th>% Vomit w/o premed</th>
</tr>
</thead>
</table>
| **High** | Cisplat $\geq$ 50/m²  
DTIC, Mustard, “AC” | $>90$            |
| **Mod** | Dox, Carbo, 
Cyclophos $<1.5g$ | 30-90            |
| **Low** | Tubulin drugs, Gem, | 10-30            |
| **Min** | Vinorelbine, Cape, 5FU | $<10$            |

Koeller. Supp Care Cancer 2002; 10:519
What are the 3 major antiemetic classes of drugs?

- **Dexamethasone**
- **5HT\textsubscript{3}RA “Setrons”: CORNERSTONE**
  - **2\textsuperscript{nd} gen**: Palonosetron 40 hr T-1/2
  - **1\textsuperscript{st} gen**: PO, IV Ondansetron, *Granisetron (also Transderm)*, Dolasetron (only PO, not IV)
- **NK\textsubscript{1} antagonists**
  - Aprepitant PO, Fosaprepitant IV
  - Casopitant in EU

Gralla R. MASCC 2004; NCCN 2010
What new mechanisms explain superiority of palonosetron to 1st generation 5HT3 RA?

Slusher B. Clin Adv Hem Oncol 2013 (Suppl1) 11:3
What new potential toxicity with Ondansetron?

- FDA Safety Announcement 9-15-11
- QTc Prolongation
  - www.qtdrugs.org
  - Torsade de Pointes
- FDA 2012:
  - Max single IV ondansetron is ≤16 mg; no change in ORAL dosing
  - Withdraw IV dolasetron
- Caution for pts with
  - Congenital QT interval prolonged
  - Low K, Mg, CHF, bradyarrhythmia
  - Concomitant drugs ↑QTc (droperidol)

www.fda.gov/Drugs/DrugSafety/ucm271913.htm
What adverse reactions of “setrons” should be addressed with patient?

<table>
<thead>
<tr>
<th>Event</th>
<th>Aloxi 0.25 mg (N=633)</th>
<th>Ondansetron 32 mg I.V. (N=410)</th>
<th>Dolasetron 100 mg I.V. (N=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>60 (9%)</td>
<td>34 (8%)</td>
<td>32 (16%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>29 (5%)</td>
<td>8 (2%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (1%)</td>
<td>7 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (1%)</td>
<td>9 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (&lt;1%)</td>
<td>4 (1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (&lt;1%)</td>
<td>3 (1%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>
What are the minor antiemetic drug classes?

- Antipsychotic: Haldoperidol, Olanzepine
- Benzodiazepine: Lorazepam
- Cannabinoid: Dronabinol, Nabilone
- Dopamine receptor antagonist: Metochlopramide
- Phenothiazine: Prochlorperazine, Promethazine
- GABA antagonists: Gabapentin

Gralla R. MASCC 2004; NCCN 2010
Why does Aprepitant require 5HT3RA ("setron")? Not effective in acute 0-24h, serotonin-mediated emesis.

Hesketh PJ Eur J Cancer 2003;39:1074
What is the Granisetron Transdermal Patch

- 34.3 mg: place 24-48h before chemo.
- Max duration 7 days; ~$285/patch
How effective is transdermal granisetron (TD) vs PO? Similar but must apply day before

- 2-Blind RCT: PO vs TD
- N=641; Nev=621
- Cisplat rx 71%
- 4-5 day rx: 32%

Safety: PO vs TD

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Const</td>
<td>3</td>
<td>6.6</td>
</tr>
<tr>
<td>H/A/T</td>
<td>0.3</td>
<td>2.5</td>
</tr>
<tr>
<td>QTc</td>
<td>0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Boccia RV. Support Care Cancer 2011; 19:1609

- Efficacy same
- Side effects differ? due to prolonged 7 day duration?
**What are HEC antiemesis guidelines?**

<table>
<thead>
<tr>
<th>DRUG, mg</th>
<th>v.1.2014</th>
<th>DAY 1</th>
<th>2-3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>NK-1 inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Aprepitant PO</td>
<td>125</td>
<td>80</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>• Fosaprepitantant IV</td>
<td>150</td>
<td>(cont PO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>5HT3 antag (&quot;setron&quot;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 2nd gen</td>
<td>Palonosetron</td>
<td>0.25</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1st gen</td>
<td>Granisetron</td>
<td>2 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolasetron</td>
<td>100 PO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>16-24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>± Lorazepam</td>
<td>IV, PO, SL</td>
<td>0.5-2.0 Q4-6H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>± H2 blocker or proton pump inhib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCCN
Olanzapine is not FDA-approved for control of nausea nor emesis... but it is effective

INDICATIONS AND USAGE

1.1 Schizophrenia
1.2 Bipolar I Disorder (Manic or Mixed Episodes)
1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder
1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania
1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder
1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

Olanzapine is effective for refractory chemotherapy-induced nausea and vomiting irrespective of chemotherapy emetogenicity

Sierra Vig · Laurel Selbert · Myke R. Green
What is unique about olanzapine?

- Atypical anti-psychotic approved ‘96
- Blocks multiple neurotransmitters
  - Dopamine: D1, D2, D3 brain
  - Serotonin: 5-HT2a, 5-HT2c, 5H-T3*, 5-HT6 (key for emesis)
- Alpha adrenergic: catecholamines
- Muscarinic: acetylcholine
- H1: Histamine
- Prevents acute & delayed emesis; rx breakthrough, refractory emesis & N
- No cytochrome P450 nor QT issues
- Toxicity limited for short courses: sedation, weight gain, elderly psycho
- NCCN: HEC-MEC substitute for NK-1; breakthrough: 10 mg PO days 1-4
What is advantage of multiple neurotransmitter blockade? Better nausea control

- Phase 3, HEC, N=241
- Palonosetron w/ Dex randomized
  Aprepitant vs Olanzapine 10 QD x 4
- Emesis control same
- Nausea less with olanzapine

Improving the Quality of Cancer Care in an Aging Population: Recommendations From an IOM Report

With 10,000 individuals reaching age 65 years each day, the incidence of cancer is expected to increase by 67% among this population from 2010 to 2030.

NEED FOR A WORKFORCE TRAINED IN GERIATRICS PRINCIPLES

Olanzapine Adverse Reactions in geriatric pts:
• Low risk of psychosis in elderly

What is a “Bad Ad?”

- Promote “off label use”
- Overstate benefits
- Omit or minimize risks
- Misleading drug comparisons

What promotions are regulated? Speaker program; TV, radio; Sales rep; Promo

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm#ExamplesofViolations
Don’t give patients starting on a chemotherapy regimen that has a low or moderate risk of causing nausea and vomiting antiemetic drugs intended for use with a regimen that has a high risk of causing nausea and vomiting.

- New, effective drugs with fewer side effects prevent chemotherapy-induced nausea & vomiting. Improved life quality, fewer changes in chemo, hospitalization avoided
- New drugs expensive; use only for high need
- If low potential for N/V, use less costly drugs


Updated 10-29-13
Anemia

Anemia of Cancer
Cancer and Chemotherapy-induced Anemia in Breast Cancer
How ESAs became non-starters

- Favorable early results of erythropoietic agents ➔ trials with expanded indications
- Widespread use: $1 billion/yr in early 2000s for “palliative” agent
- “BEST” breast cancer trial: impaired survival
- Head and neck cancer radiation trial suggested tumors have Epo receptors; impaired survival with Epo agents
- Meta-analysis: ↑ venous thromboembolism;

2010 FDA Guidelines for ESAs: REMS

- Do not use in patients receiving myelosuppressive chemo for cure: Adj Breast

- Risk Evaluation Management Strategy REMS: use in stage IV only if pt signs Informed Consent acknowledging possible ESA risks
  - Some tumors to grow faster
  - Some patients die sooner
  - Blood clots and serious heart problems (MI, heart failure) or stroke

- Understand MD has special training in use

Summarized in NCCN Guidelines ver 2.2014
www.nccn.org
Recent ESA studies: refute effects on survival, disease progression, but confirm ↑ risk venous-thromboembolism

Glaspy: meta-analysis (No. studies)
- mortality (60 studies) OR 1.06 (0.97-1.15),
- disease progression (26) OR 1.01 (0.90-1.14)
- Venous thromboemb (44) OR 1.48 (1.28-1.72)

Untch: PREPARE preop: no effect on pCR
Engert: adv Hodgkins’ BEACOPP Epo vs nil
Ludwig: meta-analysis darbepoetin vs nil

How is anemia defined & severity graded? What are main causes?

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hgb g/dl</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mild</td>
<td>10-12</td>
<td>LOSS: $H^2$</td>
</tr>
<tr>
<td>2 Mod</td>
<td>8-10</td>
<td>• Hemorrhage</td>
</tr>
<tr>
<td>3 Severe</td>
<td>6.5-8</td>
<td>• Hemolysis</td>
</tr>
<tr>
<td>4 Life-threatening</td>
<td>&lt;6.5</td>
<td>PRODUCTION: INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inflammation,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infiltrat’n,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inherited</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal, Radiation-Chemo</td>
</tr>
</tbody>
</table>

Dicato M. Ann Oncol 2010; 21(Suppl 7): vii167
What is the main cause of cancer-related anemia?

- **INFLAMMATORY CYTOKINES**
  - Impaired hematopoiesis
    - TNF-alpha, GATA-1, GATA-2
    - Role for “targeted therapy” GATA-2 inhibitors, TNFi
  - Impaired iron metabolism
    - IL-6 induced hepcidin production
    - Role for anti-hepcidin antibodies

- **Chemotherapy**
  - Impaired hematopoiesis
  - Platinum →↓ renal EPO production

Dicato M. Ann Oncol 2010; 21(Suppl 7): vii167
How do inflammatory cytokines impair iron metabolism? Hepcidin ↓ absorption

Hedenus M. Med Oncol 2008; ePub 5-18-08
How to dx ca-related anemia?
Who should be treated?

- **Hgb <11 g or ≥ 2 g below baseline**
  - If no cause identified, likely INFLAMMATORY or RX-related

- **Treatment algorithm by “risk”**
  - Asymptomatic, no comorbidities
  - Asymptomatic, hi comorbidity/risk
    - Cardiac: CHF, CAD
    - Chronic pulmonary disease
    - Cerebral vascular disease
  - Symptomatic: ↑pulse, SOB, fatigue

NCCN Guidelines v.2.2012  @  www.nccn.org
How to treat anemia? v 2.2014

Transfusion

- In Assx: Hgb 7-9 g
- In Symptomatic Pts ("tachy", ↓BP):
  - 8-10 g or alleviate sx
  - In acute coronary syndromes: ≥ 10g

ESAs: limited use

- Chronic kidney disease
- Palliative treatment cancer only with consent "REMS"
- Contraindicated for curative treatment
Who benefits from iron? NCCN v 2.2014

“Functional iron deficiency” less relevant now
- insufficient iron available for ↑ hematopoesis 2o ESAs due to inflammatory issues (hepcidin, IL-6, etc)
- “iron-restricted”; PO iron NOT effective
- Definition: Ferritin < 30-800 ng/mL AND T-sat 20-50%
- IV iron with ESA indicated

Absolute iron deficiency: Ferritin <30 ng/mL AND T-sat <20%  ➔ Iron supplement

No iron deficiency: iron will not benefit
- Ferritin >800 ng/ml OR TSAT ≥50%

If ferritin & TSAT discordant, low ferritin is determinant of benefit of IV iron
What iron preparations are available? Advantages of each?

- **Iron Dextran** *(InFeD, do not use Dexferrum due to high rate of anaphylaxis)*
- **Ferric Gluconate**: 1 g ~ $600; multiple doses
- **Iron sucrose**: 1 g ~ $600; multiple doses
- **Ferumoxytol**: 2 injections (510 mg)
  - 3-8 days apart
  - No test dose, ~ $950
  - Rapid IV infusion (1 min)
  - No anaphylaxis
  - **MOA**: PSC shell m&m
    - Shields iron from blood
    - Delivers to RES, transferrin

ANEM-E @
www.nccn.org
The Medical Letter 3-22-2010 #1334
Myelosuppression and MGF’s 
(Myeloid Growth Factors)
What are the key issues for Febrile Neutropenia (FN) & Myeloid Growth Factors (MGF)?

- What is Febrile Neutropenia
- Risk factors for FN: ANC & duration, cycle #
- What is the benefit of prophylactic MGF
- What are criteria for prophylactic MGF?
  - Tumor type, Regimen, Patient, Cure Factor
- Should MGF be used DURING FN?
- Does timing of administration of MGF after chemo matter?
- What are biosimilars?
- What new pathobiology
What defines neutropenia, febrile neutropenia & risk of CIN-FN?

- **Definition**: ANC <500/mm³ or <1000 but expected <500 w/in 48h

- **Fever**:  
  - single temp >38.3°C (101°F)  
  - temp ≥ 38.0°C for 1 hour

- Febrile neutropenia FN = F + N

- **Risk of FN increases with** ¹, ³, ⁴
  - Depth & duration of neutropenia

*Chemotherapy-induced neutropenia “CIN”*

Risk (%) FN & Infection parallels ANC depth & duration

Rahman Z. Cancer 79:1150-7, 1997

% Episodes

% Infection by ANC

Threshold: ANC < 250

Threshold < 500

ANC x 10^3/ ml
What cycle of chemotherapy is at the highest risk for Febrile Neutropenia (FN)? **Cycle 1!**

- So “wait and see” isn’t logical

Days to 1\textsuperscript{st} FN: Aggressive NHL Rx CHOP

Higher if $>65$

Peak: C\#1

C\#2

Age $\geq 65$ years

P = .0002

Age < 65 years

Lyman GH. Leuk Lymphoma 2003; 44:2069-76
What is the role of prophylactic MGFs?

To reduce risks of

- FN by 50%
- Infection-related death

Kuderer N.  P ASCO 2005 #8117
Lyman GH.  Ann Oncol 2013; 24:2475
Prophy G-CSF: 
Obs = 1/2 Expected FN

Studies = 14  
N = 3,091

<table>
<thead>
<tr>
<th>Events</th>
<th>Control</th>
<th>G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>892</td>
<td>576</td>
<td>316</td>
</tr>
</tbody>
</table>

FN Rate: 37%  20%
[35-40]  [18-22]

RR: 0.5
[0.4, 0.7]

Kuderer N. ASCO 2005 #8117
The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials

G. H. Lyman\textsuperscript{1*}, D. C. Dale\textsuperscript{2}, E. Culakova\textsuperscript{1}, M. S. Poniewierski\textsuperscript{1}, D. A. Wolff\textsuperscript{1}, N. M. Kuderer\textsuperscript{1}, M. Huang\textsuperscript{1} & J. Crawford\textsuperscript{1}

\textsuperscript{1}Department of Medicine, Duke University, Durham; \textsuperscript{2}Department of Medicine, University of Washington, Seattle, USA

- 59 randomized comparisons of chemo with or without initial G-CSF support (adults)
- Patients: G: 11,337; no G: 13,456
- Median f/u: average 37 mo (7-188)
- Deaths: G: 4251; no G 5188
- RR all cause mortality: 0.93 (0.90-0.96; \textit{P}<0.001)
What are criteria for prophylactic MGF?

- **Chemo**: >20% risk of FN is cost-effective: Dose Dense AC; TAC; Docetaxel-trastuzumab

- **Patient risk factors:**
  - age >65; poor performance status
  - Impaired bone marrow function: extensive prior chemo/XRT; BM tumor
  - High WBC demand: ongoing infection, open wounds, recent surgery, nutrition
  - Organ dysfunction: renal, liver, COPD, CHF

- **Intent**: cure or palliation?
Decision Tree for Primary Prophylaxis
NCCN v2.2013

1 Evaluate
- Disease
- Chemo Regimen
- Pt Risk Factors
- Treatment Intent

2 Assess Risk*
- High > 20%
- Intermediate 10–20%
- Low 10%

3 Intervene
- Use CSF
- Maybe
- No

* Risk of FN or neutropenic event compromising treatment
Don’t use white cell stimulating factors for primary prevention of febrile neutropenia in patients with less than 20 percent risk for this complication.

• If equally effective regimen with less risk available, use it
• Exceptions: high risk patients (as defined above)
At what % FN is Pegfilgrastim cost-effective? “20% Trial”

- **Aim**: Show ↓↓ FN when PegF given with 1\textsuperscript{st} \& all later cycles in regimen that causes 20\% NF
- Docetaxel 100 mg/m\textsuperscript{2} Q3 wk x4
- Double-blinded, placebo-control
- Multicenter
- Stratify by disease

Vogel CL. J Clin Oncol 2005; 23:1178
What % decrease in FN did prophy PegF confer if baseline risk is 20% FN?

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>PegF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>465</td>
<td>463</td>
<td></td>
</tr>
<tr>
<td>% Febr Neut*</td>
<td>17</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%FN Hosp**</td>
<td>14</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% IV anti-infec#</td>
<td>10</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

60% FN occur in cycle 1 in Placebo pts
*94% reduction; ** 93% ↓; #80%↓

Vogel CL. J Clin Oncol 2005; 23:1178
What is role & safety of prophylactic antibiotics during neutropenia to prevent bacterial infection?

Effective, safe, RECOMMENDED!


Cochrane meta-analysis 10-05

Effective: reduced

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths</td>
<td>0.66</td>
<td>0.54-0.81</td>
</tr>
<tr>
<td>Infection-related deaths</td>
<td>0.58</td>
<td>0.45-0.74</td>
</tr>
<tr>
<td>Quinolones</td>
<td>0.52</td>
<td>0.37-0.84</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>0.78</td>
<td>0.75-0.82</td>
</tr>
</tbody>
</table>

NNT* to prevent 1 death = 60 34-268

Safe: no sig toxicities, resistance

*NNT: No. needed to treat.  
15Gafter-Cvili. Cochrane Database 2005; 4:CD004386
Is MGF given SAME day as chemo as effective as NEXT day?

- Most studies performed with NEXT day schedule
- Most studies show: NEXT day better
- Limited studies (2 retrospective, 1 prospective) show “no difference”
- **Recommendation:**
  - Next day
  - 3-4 days later
  - “special circumstances” same day

NCCN v 2.2013
Pegfilgrastim Dosing on Same Day as Myelosuppressive Chemotherapy for Ovarian or Primary Peritoneal Cancer

Samer I. Schuman, MD, Nicholas Lambrou, MD, Katie Robson, ARNP, Stefan Glück, MD, Nikolaos Myriounis, MD, J. Matt Pearson, MD, and Joseph A. Lucci III, MD

- Retrospective, 5/03 – 6/06; single arm
- n=46 Gyn
- No Gr 4 neutropenia, FN, hospitalization, dose delay, dose reduction
- “Same day administration…convenient, safe, effective”

Schuman SJ. J Support Oncol 2009; 7:225-228
Phase II: Same vs. Day 2 PegF with TAC Results
Kaufman PA. Dartmouth, NH

<table>
<thead>
<tr>
<th>Day of PegF</th>
<th>Duration ANC &lt;500/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>1.4 days</td>
</tr>
<tr>
<td>Same day</td>
<td>2.6 days</td>
</tr>
</tbody>
</table>

Mean difference = 1.2 days (95% CI: 0.7, 1.6)
## Phase II: Same vs. Day 2 PegF with TAC

### Kaufman PA. Dartmouth, NH

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Same day</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 45</td>
<td>N = 45</td>
</tr>
<tr>
<td>1</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>3</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>All</td>
<td>33%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Conclude: Day 2 more effective!
If patient presents with FN do you give MGFs?

- If received Pegfilgrastim ➔ NO BENEFIT
  - Pegfilgrastim levels are high if ANC is low
- If receiving daily MGF ➔ continue past nadir
- If did not receive MGF and high risk for complications (below) YES
  - sepsis syndrome, ANC < 100, age > 65, pneumonia, ANC < 500 for 10+ days, invasive fungus, documented infection, prior FN, hospitalization

NCCN v 2.2013
“Biosimilar” “interchangeable”
tbo-filgrastim
What is tbo-filgrastim?

- Leukocyte growth factor; Teva Pharma
- "biosimilar" filgrastim
- Secreted by genetically engineered E.coli: non-glycosylated recombinant methionyl form of human G-CSF
- Approved EU 2008; FDA 8/29/2012
- Same indications, dosing as filgrastim
- 2 phase I trials in health subjects
- 3 phase 3 trials: breast (pivotal), lung, Non-Hodgkins lymphoma

www.FDAdrugs.gov
What did the pivotal (breast) trial show?

- 12/04-9/05; 10 countries
- “AT” Doxorubicin 60, Docetaxel 75 mg/m²
- Randomized 2:2:1 to tbo-filgrastim (n=130), filgrastim (136), placebo (70)
  - After C#1, placebo switched to tbo-filgr
- AIM: days of severe neutropenia, DSN
- PATIENTS: Stage II-IV breast cancer
- RESULTS: Days of Severe Neutropenia
  - Tbo-Filgrastim: 1.1
  - Filgrastim: 1.1
  - Placebo: 3.9

Del Giglio A. BCM Cancer 2008; 8:332
What was the difference in days of severe neutropenia DSN? No difference
Chemo-induced neuropathy impairs hematopoietic regeneration by injury to BM stem cell niche.

- Sympathetic nerves innervate BM
- release norepi (NE)
- NE binds adrenergic receptors (AR) of “niche” cells, the microenvironment of hematopoietic stem cell (HSC)
- Niche cells: CXCL12+, Endothelial cells (EC)
- Neurotoxic chemo injures!
- Role for neuroprotectants!

Summary & Conclusions

See slides 1-3!
THANK YOU! 😊

A retentive memory is a good thing,
But, the ability to forget is the true token of greatness
--Hubbard d. 1915
Thank you for the Brain Food, Joyce, PER, and Colleagues.