Targeting Supportive Care:
Emesis  Anemia  Myelosuppression

What you will be to your patients if you hit the target!

Frankie Ann Holmes
US Oncology
Houston TX
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: 5HT3-RA + NK1-RA + DEX

• “Emesis risk period” = 5 days, 1-5

• 3 classes of major antiemetics:
  ➢ 5HT3 receptor antagonists (5HT3-RA);
  ➢ Steroids;
  ➢ NK-1 Receptor Antagonists (NK1-RA)
EMESIS cont’d

• Palonosetron’s binding characteristics & chemistry make it superior to 1\textsuperscript{st} generation 5HT3-RA

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

• Most potent antiemetic combination = 1 from each class: palonosetron, NK1-RA, dexamethasone

• Olanzapine, not FDA approved, can substitute for NK1-RA, controls breakthrough, refractory N/V

• GERD \textit{rx} and non-drug causes (diet)

• Some pts have more N/V than predicted (genetics!)
MYELOSUPPRESSION & MGF’s (aka CSF’s)

- Cycle 1 is highest risk for FN
- Use MGFs for regimens with 20%+ risk FN, hi risk pts (old, organ dysfnc, wound)
- 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
- Loratadine 10 BID controls bone pain
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; new drugs soon
- Treat correctable causes, iron deficiency
- Transfuse if symptomatic
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; v2014.2
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 2° drugs, diabetes
- EMOTIONAL: anticipatory, anxiety
- NEURO: Brain, LMD mets
- DRUGS, DIET: Opioids, Antibiotics; Hot, spicy
- SEX: Estradiol

www.nccn.org; v2014.2
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 active receptor!
Where are the receptors for these neurotransmitters located?

**Brain stem (medulla):**
- 5-HT3R (serotonin)
- NK1R (Substance P)
- D2R (dopamine)

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

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Slusher B. Clin Adv Hem Oncol 2013 (Suppl1) 11:3
### How is emesis graded? Hesketh Levels

<table>
<thead>
<tr>
<th>Grade</th>
<th>Drugs (doses in mg/m²)</th>
<th>% Vomit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi HEC</td>
<td>AC, Cyclo &gt;1.5, Doxorub &gt;60, Epi &gt;90, Cisplat</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Mod MEC</td>
<td>Carboplat, Cyclo &lt;1.5, Dox &lt;60, Epi &lt;90; PO Cyclo &gt;100</td>
<td>30-90%</td>
</tr>
<tr>
<td>Low LEC</td>
<td>Ado-trastuz, Microtubule, FU, Gem, Cape, Cyclo &lt;100, Lapat, Everolimus, Ruxolit</td>
<td>10-30%</td>
</tr>
<tr>
<td>MinEC</td>
<td>Bevaciz, Pertuz, Trastuz, Vinorelbine, Dasatinib</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

What are the 3 major antiemetic classes of drugs?

- **Steroids:** Dexamethasone
- **5HT\textsubscript{3}RA “Setrons”:** CORNERSTONE
  - \textsuperscript{2\textsuperscript{nd} gen}: Palonosetron 40 hr T-1/2
  - \textsuperscript{1\textsuperscript{st} gen}: PO, IV Ondansetron, *Granisetron (also Transderm), Dolasetron (only PO, not IV)
- **NK\textsubscript{1} RA**
  - Aprepitant PO, Fosaprepitant IV
  - Casopitant in EU
  - Netupitant→oral combination w/ Palonosetron
    FDA approved “NEPA” 10/2014

What new mechanisms explain superiority of palonosetron to 1st generation 5HT3 RA?

<table>
<thead>
<tr>
<th>All 5-HT3 RA</th>
<th>PALONOSETRON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competitive Binding</td>
<td>Allosteric Binding</td>
</tr>
<tr>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>

Slusher B. Clin Adv Hem Oncol 2013 (Suppl1) 11:3
What are the minor antiemetic drug classes?

- Antipsychotic: Haldoperidol, Olanzepine
- Benzodiazepine: Lorazepam
- Cannabinoid: Dronabinol, Nabilone
- Dopamine receptor antagonist: Metochlopramide
- Phenothiazine: Prochlordperazine (not IV), Promethazine
- GABA antagonists: Gabapentin (some recent data dispute)

Gralla R. MASCC 2004; NCCN 2010
### What are the NCCN Antiemesis Guidelines v2.2014

<table>
<thead>
<tr>
<th>Grade</th>
<th>% Emesis w/o med</th>
<th>5HT3-RA</th>
<th>DEX</th>
<th>NK1-RA*</th>
<th>Other**</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEC¶</td>
<td>&gt;90%</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>MEC</td>
<td>30-90%</td>
<td>✔</td>
<td>✔</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>LEC</td>
<td>10-30%</td>
<td>-</td>
<td>✔</td>
<td>-</td>
<td>***</td>
</tr>
<tr>
<td>minEC</td>
<td>&lt;10%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>§</td>
</tr>
</tbody>
</table>

*NK1-RA or Olanzapine; ¶need 5 day coverage

**Other: Lorazepam; Proton Pump Inhibitor/H2 Blocker

***Dex 12 or Metocloproamide 10-40 PO/IV or 5HT3-RA PO and Other**; § No routine prophylaxis

Anticipatory nausea irrespective of Grade: Lorazepam

[www.nccn.org](http://www.nccn.org)
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

What toxicities do anti-emetics cause?

- Phlebitis w/ Fosaprepitant peripheral IV: AC > cddp
  - Mayo 2011
    - CDDP n=81
    - AC n=99
    - Swelling: 3% (CDDP), 12% (AC)
    - Infusion site pain: 0% (CDDP), 27% (AC)
    - Erythema: 0% (CDDP), 22% (AC)
    - Phlebitis/Thromboph: 3% (CDDP), 5% (AC)

- QTc prolongation with Ondansetron
- H/A
- Constipation

Hegerova LT. Supp Care Cancer 2014; doi 10.1007/s00520-014-2326-9 (June 2014)
What adverse reactions of “setrons” should be addressed with patient?

<table>
<thead>
<tr>
<th>Event</th>
<th>Palo 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>

Updated 7-2013 http://www.aloxi.com/docs/pdf/PI.pdf
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>5HT3R developed; 3 agents; equivalence; IV=PO</td>
</tr>
<tr>
<td>Late 90s</td>
<td>Dexamethasone key for delayed emesis</td>
</tr>
<tr>
<td>2003</td>
<td>FDA approves NK1-RA PO aprepitant</td>
</tr>
<tr>
<td>1-29-08</td>
<td>FDA approves NK1-RA IV fosaprepitant</td>
</tr>
<tr>
<td>9-15-08</td>
<td>FDA approves Granisetron 5 day patch “Sancuso”</td>
</tr>
<tr>
<td>12-17-11</td>
<td>FDA warns QTc prolongation: Torsade de Pointes; Dolasetron¹; <a href="http://www.qtdrugs.org">www.qtdrugs.org</a></td>
</tr>
<tr>
<td>2011</td>
<td>NCCN Guide changed “AC” to “HEC”</td>
</tr>
<tr>
<td>6-29-2012</td>
<td>Max single dose IV Ondansetron $\leq 16$ mg;² PO dose 24 mg; IV Dolasetron no longer used</td>
</tr>
</tbody>
</table>


What is the Granisetron Transdermal Patch

- 34.3 mg: place 24-48h before chemo.
- Max duration 7 days; ~$285/patch
**What’s new?**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-13</td>
<td>NCCN: Olanzapine 10 mg PO D1-4 is alternative to NK1-RA</td>
</tr>
<tr>
<td>1-10-14</td>
<td>Roila: D2, 3, Dex efficacy = Aprep in AC</td>
</tr>
<tr>
<td>2-14</td>
<td>NCCNv2.2014: Multiday HEC regimens: repeat Aprep D3-5; Palo D1 &amp; D3</td>
</tr>
<tr>
<td></td>
<td>Albany C. JCO 2012; 30:3998</td>
</tr>
<tr>
<td>8-14</td>
<td>Santana: Meta-analysis: adjunctive non NK1-RA &amp; non 5HT3-RA may be useful</td>
</tr>
<tr>
<td>9-14</td>
<td>Raftopoulos: APF530 extended release subcu administration Granisetron</td>
</tr>
<tr>
<td>10-10-14</td>
<td>FDA approves Netupitant-Palonosetron fixed dose combo PO; Day 1 only but 5 Day effects</td>
</tr>
</tbody>
</table>

Phase 3: NEPA, fixed dose netupitant and palonosetron for prevention of CINV during repeated cycles of MEC

- AC still classified as “MEC”
- 177 sites in 15 countries
  - Rugo UCSF!

** Oral NEPA + Oral DEX 12 mg**
(NEPA = NETU 300 mg + PALO 0.50 mg)

** Oral PALO 0.50 mg + Oral DEX 20 mg **

- NEPA or PALO: ingested 60 min prior to chemotherapy; DEX: 30 min prior to chemotherapy
- NO antiemetics given after Day 1
Characteristics of NEPA Components

**NETUPITANT**
- Selective neurokinin type 1 receptor antagonist (NK₁ RA)¹
- Competitively binds to and blocks activity of human substance P receptors¹
- High binding affinity, long half-life (90 h)¹,²
- High (>90%), long-lasting (>96 h) brain receptor saturation after single oral dose¹

**PALONOSETRON**
- Higher binding affinity and longer half-life than other 5-HT₃ RAs²
- Exhibits distinctly different receptor binding (allostERIC binding, positive cooperativity)³
- Results in long-lasting inhibition of 5-HT₃ receptor function³
- Inhibits cross-talk between the 5-HT₃ and NK₁ receptor pathways³
- Antiemetic guideline-recommended “preferred” 5-HT₃ RA⁴

²Data on file
³Rojas et al. J Pharmacol Exp Ther 2010;335(2):362-368
Conclusions

- NEPA superior 0-120 hr complete response over all cycles vs oral PALO; also emesis & nausea
- Low incidence treatment-related AE
- SINGLE PO fixed dose D1
What challenges persist?

- Nausea – less well controlled, different paths

- Cost: Olanzapine vs NK1-RA; Dex vs NK1-RA

- Pharmacogenomics
  - 5HT3R subunits A, B polymorphisms
  - CYP2D6 polymorphisms: rapid, ultrarapid metabolisers
  - MDR1 (ABCB1) polymorphism

- Compliance

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1 Celio L. JCO doi:10.10.1200/JCO.2012.47.2209;
2 Roila F. JCO 2013; 32:1010. Aprepitant €60; Dex €3.
What is the adherence to anti-emesis guidelines? 57%

- 70% women; Br Ca 48%; eHR study; HEC 1/3
- Better results if Guideline Consistent (GCCP):

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GCCP</th>
<th>Not</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall N=742</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CINV N=460</td>
<td>53%</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No emesis N=835</td>
<td>91%</td>
<td>87%</td>
<td>0.027</td>
</tr>
<tr>
<td>No clin sig N N=1,295</td>
<td>53.5%</td>
<td>44.5%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Anemia
Anemia of Cancer

ESA

HCP Program Starter Kit
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 2.2015 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><strong>LOSS:</strong> $H^2$</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><strong>PRODUCTION:</strong></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: direct effects
  - Impaired hematopoiesis
  - Platinum \(\rightarrow\) renal EPO production

Dicato M. Ann Oncol 2010; 21(Suppl 7): vii167
Why do we need IV iron if the duodenum is intact?

Hepcidin impairs iron absorption

Andrews N. NEJM 1999; 341:1986
How do inflammatory cytokines impair iron metabolism? Hepcidin \(\downarrow\) absorption

Hedenus M. Med Oncol 2008; ePub 5-18-08
Hepcidin modulates iron metabolism

Liver sinusoids
- Kupfer cells (K)
- Endothelial cell
- Fe or microbes
- Release IL6
- liver ➔ hepcidin

Hepcidin ➔ available Fe:
- ➔ duodenal absorption
- ➔ macrophage release
Lexaptepid binds & neutralizes hepcidin

1\textsuperscript{st} in human volunteer study; 24 healthy men

Acute inflammation model: IV endotoxin

30 min later, placebo vs Lexaptepid

Aim: 1) serum iron level @ 9 h \textcolor{red}{\textbf{increased}}

\hspace{3cm}2) effect on immune system response \textcolor{red}{\textbf{none}}

Conclude: Promising agent for anemia of chronic disease due to hepcidin
Plasma lelaptepid and iron parameters during experimental human endotoxemia.

How to dx ca-related anemia? Who should be treated?

- Hgb < 11 g or ≥ 2 g below baseline
  - If no cause identified, likely INFLAMATORY 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.2.2015 @ www.nccn.org
If anemia is not due to absolute or functional iron deficiency, there are currently only two proven methods of improving Hb: ESAs and red blood cell transfusion. Listed below are risks and benefits of each method.

<table>
<thead>
<tr>
<th>ESA in the Cancer Setting</th>
<th>Red Blood Cell Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks</strong></td>
<td>• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury)</td>
</tr>
<tr>
<td></td>
<td>• TACO</td>
</tr>
<tr>
<td></td>
<td>• Virus transmission (eg, hepatitis, HIV)</td>
</tr>
<tr>
<td></td>
<td>• Bacterial contamination</td>
</tr>
<tr>
<td></td>
<td>• Iron overload</td>
</tr>
<tr>
<td></td>
<td>• Increased thrombotic events</td>
</tr>
<tr>
<td></td>
<td>• Possible decreased survival</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>• Rapid increase of Hb and hematocrit levels</td>
</tr>
<tr>
<td></td>
<td>• Rapid improvement in anemia-related symptoms</td>
</tr>
</tbody>
</table>
Transfusion

- In Assx: Hgb 7-8 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"
- Special situations: Jehovah’s witness
- Contraindicated for curative treatment
Who benefits from iron? NCCN v 2.2015

- “Functional iron deficiency” Stored iron sufficient but not bioavailable due to infection/inflammatory issues (hepcidin, IL-6, etc) or demands of ESA administration
  - “iron-restricted”; PO iron NOT effective
  - Definition: Ferritin < 30-800 ng/mL AND T-sat 20-50%
  - If receiving ESA, IV iron is 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); $950
  - 3-8 days apart; no test dose
  - Rapid IV infusion (1 min)
  - MOA: PSC shell m&m
    - Shields iron from blood
    - Delivers to RES, transferrin
- **Ferric Carboxymaltose**: 750 mg
  - 2 injections 7 d apart; $1500

www.nccn.org
The Medical Letter 3-22-2010 #1334
12-9-13 #1431
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**\(^1\): ANC <500/mm\(^3\) or <1000 but expected <500 w/in 48h

- **Fever**\(^2\):
  - single temp >38.3\(^\circ\)C (101\(^\circ\)F)
  - temp ≥ 38.0\(^\circ\)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
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\(^{st}\) FN: Aggressive NHL Rx CHOP

Higher if >65
Peak: C\#1

C\#2

Age ≥ 65 years

Age < 65 years

P = .0002

Days to First Febrile Neutropenia Episode

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:

Risk in Control Group
Risk in G-CSF Group

<table>
<thead>
<tr>
<th>Studies</th>
<th>N = 3,091</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Control</td>
</tr>
<tr>
<td>892</td>
<td>576</td>
</tr>
<tr>
<td>FN Rate</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>[35-40]</td>
</tr>
</tbody>
</table>

RR: 0.5 [0.4, 0.7]

Obs = 1/2 Expected FN

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. Lyman¹*, D. C. Dale², E. Culakova¹, M. S. Poniewierski¹, D. A. Wolff¹, N. M. Kuderer¹, M. Huang¹ & J. Crawford¹

¹Department of Medicine, Duke University, Durham; ²Department 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; 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
  - HIV infection

- **Intent:** cure or palliation?

Aapro MS. Eur J Cancer 2011; 47:8-32  www.nccn.org
Decision Tree for Primary Prophylaxis
NCCN v2.2014

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)

Why do we have “standards of care” without evidence of patient benefit?

9/2012: www.choosingwisely.org
At what % FN is Pegfilgrastim cost-effective?? “20% Trial”

- **Aim:** Show ↓↓ FN when PegF given with 1st & all later cycles in regimen that causes 20% NF
- **Docetaxel** 100 mg/m² 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
Robin Roberts: I'm Going to Beat This
June 11, 2013
By ROBIN ROBERTS via GOOD MORNING AMERICA

Nora Ephron Dies at 71; Writer and Filmmaker With a Genius for Humor
6-27-2012
Is risk of AML/MDS ↑ with CSF? Yes, but ...

**RR 1.92**

Lyman GH JCO 2010; 28:2914  N=12,804: 6,058 CSF+ (44 AML-MDS), 6,746 CSF no (22); med f/u 60, 53 mo;
But risk of AML 2o CSF offset by all deaths

<table>
<thead>
<tr>
<th>Study name</th>
<th>MH risk ratio</th>
<th>Z value</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burton</td>
<td>0.936</td>
<td>-0.978</td>
<td>0.821</td>
<td>1.068</td>
<td>.328</td>
</tr>
<tr>
<td>Diehl</td>
<td>0.660</td>
<td>-2.157</td>
<td>0.452</td>
<td>0.963</td>
<td>.031</td>
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<tr>
<td>Doorduijn</td>
<td>0.975</td>
<td>-0.333</td>
<td>0.838</td>
<td>1.134</td>
<td>.739</td>
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<tr>
<td>Pan</td>
<td>1.385</td>
<td>0.397</td>
<td>0.277</td>
<td>6.913</td>
<td>.692</td>
</tr>
<tr>
<td>Pettengell</td>
<td>0.951</td>
<td>-0.274</td>
<td>0.665</td>
<td>1.360</td>
<td>.784</td>
</tr>
<tr>
<td>PfreundB1</td>
<td>0.717</td>
<td>-2.026</td>
<td>0.520</td>
<td>0.989</td>
<td>.043</td>
</tr>
<tr>
<td>PfreundB2</td>
<td>0.845</td>
<td>-2.300</td>
<td>0.732</td>
<td>0.975</td>
<td>.021</td>
</tr>
<tr>
<td>Verdonck</td>
<td>0.862</td>
<td>-1.277</td>
<td>0.687</td>
<td>1.083</td>
<td>.202</td>
</tr>
<tr>
<td>Zinzani</td>
<td>0.970</td>
<td>-0.144</td>
<td>0.637</td>
<td>1.476</td>
<td>.886</td>
</tr>
<tr>
<td>Pfreundschuh</td>
<td>0.995</td>
<td>-0.022</td>
<td>0.625</td>
<td>1.584</td>
<td>.983</td>
</tr>
<tr>
<td>Gisselbrecht</td>
<td>0.813</td>
<td>-1.085</td>
<td>0.559</td>
<td>1.182</td>
<td>.278</td>
</tr>
<tr>
<td>Burnell</td>
<td>0.818</td>
<td>-1.204</td>
<td>0.590</td>
<td>1.134</td>
<td>.228</td>
</tr>
<tr>
<td>Citron</td>
<td>0.828</td>
<td>-1.999</td>
<td>0.689</td>
<td>0.996</td>
<td>.046</td>
</tr>
<tr>
<td>Fumoleau</td>
<td>1.049</td>
<td>0.218</td>
<td>0.884</td>
<td>1.607</td>
<td>.828</td>
</tr>
<tr>
<td>Papaldo</td>
<td>0.938</td>
<td>-0.358</td>
<td>0.659</td>
<td>1.334</td>
<td>.720</td>
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<tr>
<td>Therasse</td>
<td>1.009</td>
<td>0.095</td>
<td>0.834</td>
<td>1.222</td>
<td>.925</td>
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<tr>
<td>Venturini</td>
<td>0.890</td>
<td>-0.957</td>
<td>0.701</td>
<td>1.130</td>
<td>.339</td>
</tr>
<tr>
<td>Veyret</td>
<td>1.171</td>
<td>0.630</td>
<td>0.717</td>
<td>1.913</td>
<td>.529</td>
</tr>
<tr>
<td>Fossa</td>
<td>0.849</td>
<td>-0.800</td>
<td>0.568</td>
<td>1.269</td>
<td>.424</td>
</tr>
<tr>
<td>Fleming1</td>
<td>1.027</td>
<td>0.532</td>
<td>0.932</td>
<td>1.131</td>
<td>.595</td>
</tr>
<tr>
<td>Fleming2</td>
<td>0.849</td>
<td>-2.532</td>
<td>0.748</td>
<td>0.964</td>
<td>.011</td>
</tr>
<tr>
<td>Sternberg</td>
<td>0.868</td>
<td>-2.352</td>
<td>0.772</td>
<td>0.977</td>
<td>.019</td>
</tr>
<tr>
<td>Fukuoka</td>
<td>0.969</td>
<td>-0.565</td>
<td>0.868</td>
<td>1.082</td>
<td>.572</td>
</tr>
<tr>
<td>Gatzemeier</td>
<td>0.970</td>
<td>-0.651</td>
<td>0.884</td>
<td>1.064</td>
<td>.515</td>
</tr>
<tr>
<td>Woll</td>
<td>0.807</td>
<td>-1.510</td>
<td>0.610</td>
<td>1.066</td>
<td>.131</td>
</tr>
<tr>
<td>Overall</td>
<td>0.897</td>
<td>-4.765</td>
<td>0.857</td>
<td>0.938</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

RR 0.897

Lyman GH JCO 2010; 28:2914 N=12,804: 6,058 CSF+ (1,845 died), 6,746 CSF no (2,099 died); med f/u 4-5y
What is role & safety of prophylactic antibiotics during neutropenia to prevent bacterial infection?

Effective, safe, RECOMMENDED!


### Cochrane meta-analysis 10-05\(^{15}\)

<table>
<thead>
<tr>
<th>Effective:</th>
<th>reduced</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>
<td></td>
</tr>
<tr>
<td>Infection-related deaths</td>
<td>0.58</td>
<td>0.45-0.74</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>0.52</td>
<td>0.37-0.84</td>
<td></td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>0.78</td>
<td>0.75-0.82</td>
<td></td>
</tr>
</tbody>
</table>

NNT* to prevent 1 death = 60 34-268

**Safe:** no sig toxicities, resistance

\(^{*}\text{NNT: No. needed to treat.}^{15}\text{Gafter-Cvili. Cochrane Database 2005; 4:CD004386}\)
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

Mean difference = 1.2 days (95% CI: 0.7, 1.6)
<table>
<thead>
<tr>
<th>Cycle</th>
<th>Same day</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<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 healthy 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/m^2
- 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

Del Giglio A. BCM Cancer 2008; 8:332
New Pathophysiology of the Bone Marrow

- Bone marrow neuropathy
- MGF-induced bone pain
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!

Severe pegfilgrastim-induced bone pain completely alleviated with loratadine: A case report

Cristina Romeo¹, Quan Li² and Larry Copeland³

• Who are most affected? young, taxanes, breast/lung ca, Afr Amer
• How does this relate to MGF MOA?

How do MGFs work?
3 paths: JAK, MAPK, PI3K

Lambertini M. Crit Rev Hem Onc 2014; 89:112
Why does Pegfilgrastim cause bone pain? 4 reasons

Ongoing trials: NCT 01712009 Nolan: Naproxen or Loratidine and Pegfilgrastim, start 11/12, N=600
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
Go for it, you Super Heroes!
ADDITIONAL SLIDES
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 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 breakthru, 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; breakthru: 10 mg PO days 1-4