Clinical Impact of primary prophylaxis for FN in breast cancer patients

Prof. Young Jin Suh
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Objectives

• Describe the prevalence of febrile neutropenia in patients with breast cancer
• Assess the consequences of febrile neutropenia
• Implement appropriate, guideline-based risk assessment and primary and secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) into clinical practice
### Toxicity Grading for Neutropenia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; LLN to 1.5 x 10⁹/L</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 1.5 to 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 1.0 to 0.5 x 10⁹/L</td>
</tr>
<tr>
<td>4</td>
<td>Life threatening</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 0.5 x 10⁹/L*</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; LLN, lower limit of normal.

*Grade 4 neutropenia is commonly expressed as “ANC < 500”.*
Definition of Febrile Neutropenia

Fever

Single oral temperature
> 38.3°C or
temperature
> 38.0°C over
1-2 hours

Grade 4 Neutropenia

ANC < 500
or ANC < 1,000
and expected to
fall to < 500
within 48 hours

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Definitions by consensus guidelines

• NCCN
  – Febrile neutropenia is defined as, single temperature: 38.3°C orally or 38.0°C over 1 h
  – Neutropenia: <500 neutrophils/μl or <1,000 neutrophils/μl and a predicted decline to 500/μl over the next 48 h.

• ASCO
  – Primary prophylaxis
    • First and subsequent-cycle use of prophylactic antibiotics or growth factors
  – Secondary prophylaxis
    • Addition of growth factors for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received)
Filgrastim should be administered **daily for up to 2 weeks**, until the ANC has reached $10 \times 10^9/L$ following the expected chemotherapy-induced neutrophil nadir.

The Impact of Pegylation

- **Filgrastim**
  - **NEUPOGEN®** (filgrastim) is administered as a daily subcutaneous injection starting no earlier than 24 h after administering chemotherapy.
  - The serum half-life is ~3.5 h, which necessitates daily injections to sustain neutrophil responses.

- **Pegfilgrastim (Neulasta®)**
  - **Pegylation** of filgrastim leads to reduced renal clearance and sustained plasma concentration, which result in:
    1. Once-per-cycle subcutaneous dosing
    2. Self-regulated neutrophil-mediated clearance
  - Neulasta is given as a 6-mg fixed dose appropriate for adult patients across a wide range of body weights (≥ 45 kg)
  - Neulasta is given once per cycle and should not be administered in the period between 14 days before and 24 h after cytotoxic chemotherapy.

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Neulasta serum level vs. ANC after single 6-mg Neulasta dose (n = 73)*

*Data from a fixed-dose, randomized, double-blind study. Included 157 patients with breast cancer receiving 4 cycles of doxorubicin and docetaxel (60 mg/m² and 75 mg/m², respectively). Patients received either a single fixed dose of Neulasta (6 mg) or daily injections of Neupogen (5 mcg/kg/day) 24 hours later. Patients reported in this graph received a single fixed dose of Neulasta (6 mg) approximately 24 hours after chemotherapy.

Febrile Neutropenia in Patients With Breast Cancer
Risk Through All Cycles of Therapy

Timing of first febrile neutropenia event in breast cancer patients who experienced febrile neutropenia*

67%  
First Cycle  
(n = 52)

33%  
Cycles 2-4  
(n = 26)

Phase 3 Trial†  
(n = 78)

*Patients who received docetaxel without G-CSF support (placebo-treated patients).
†Febrile neutropenia = body temperature ≥ 38.2°C and ANC < 0.5 x 10^9/L.

Febrile Neutropenia in Community Practice

Incidence of febrile neutropenia in the first 3 cycles of chemotherapy in a nationwide prospective registry with 2,692 cancer patients with select tumor types

SCLC, small cell lung cancer; NHL, non-Hodgkin lymphoma.
*Febrile neutropenia = ANC < 1.0 x 10^9/L and fever or infection.

Hospitalizations by Febrile Neutropenia

Mean length of stay in an observational retrospective cohort study of cancer patients with select tumor types hospitalized with neutropenia plus infection

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Days of Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBC (n = 37)</td>
<td>5.5</td>
</tr>
<tr>
<td>MBC (n = 37)</td>
<td>7.7</td>
</tr>
<tr>
<td>Lung Cancer (n = 96)</td>
<td>9.5</td>
</tr>
<tr>
<td>NHL (n = 178)</td>
<td>12.0</td>
</tr>
</tbody>
</table>

ESBC, early-stage breast cancer; MBC, metastatic breast cancer; NHL, non-Hodgkin lymphoma.

Importance of Dose Intensity with CMF

Figure 2. Relapse-free Survival (Panel A) and Overall Survival (Panel B) According to the Percentage of the Optimal Dose Administered.

Primary Prophylaxis

Primary prophylaxis
First and subsequent-cycle use of prophylactic antibiotics or growth factors

• Its all about prevention.

• Prevent FN, hospitalizations, infection-related deaths.

• Prophylactic use of G-CSF reduces the incidence, length, and severity of chemotherapy-induced neutropenia in breast cancer patients.
**[Pegfilgrastim vs. Placebo]**

Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial

Neulasta starting with the first cycle of chemotherapy to decrease the incidence of FN in breast cancer patients receiving docetaxel* (N = 928)

**Randomization**

- **Neulasta 6 mg SC† (n = 463)**
- **Placebo injection SC† (n = 465)**

**Primary endpoint**
- Incidence of FN‡

**Secondary endpoints**
- Hospitalizations for FN
- Anti-infective use for FN
- Safety

FN, febrile neutropenia; SC, subcutaneous.

*All patients received docetaxel 100 mg/m² IV every 3 weeks, for up to 4 cycles.
†Neulasta or placebo was administered once per cycle, on the day after chemotherapy.
‡Febrile neutropenia was defined as ANC < 0.5 x 10⁹/L and temperature ≥38.2°C.

Results

Overall incidence of febrile neutropenia, related hospitalization, and IV anti-infective use

*Febrile neutropenia = ANC < 0.5 x 10^9/L and temperature ≥ 38.2°C.

Safety

• Most adverse events occurred with equal frequency in the Neulasta and placebo groups:
  – Alopecia
  – Fever
  – Nausea, vomiting, diarrhea

• Discontinuation for adverse events occurred in:
  – 5% Neulasta patients
  – 4% placebo patients

• Bone pain, a known adverse event with Neulasta, occurred as follows:

<table>
<thead>
<tr>
<th>Bone Pain Severity</th>
<th>Neulasta (n = 463)</th>
<th>Placebo (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All reports on bone pain (mild, moderate, severe)</td>
<td>146 (31%)</td>
<td>126 (27%)</td>
</tr>
<tr>
<td>Severe bone pain</td>
<td>11 (2%)</td>
<td>6 (1%)</td>
</tr>
</tbody>
</table>

Impact of Primary Prophylaxis With Granulocyte Colony-Stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: A Systematic Review

Nicole M. Kuderer, David C. Dale, Jeffrey Crawford, and Gary H. Lyman
Study Design

• Comprehensive systematic review and meta-analysis of all reported RCTs comparing primary prophylactic G-CSF with placebo or untreated controls.
• Included adult patients with solid tumors and malignant lymphoma.
• Seventeen RCTs were identified including 3,493 patients.

Febrile Neutropenia

<table>
<thead>
<tr>
<th>Type</th>
<th>Citation</th>
<th>Treated Rate</th>
<th>Control Rate</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Crawford</td>
<td>0.400</td>
<td>0.769</td>
<td>0.520</td>
<td>0.398 to 0.680</td>
<td>.000</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Pettengell</td>
<td>0.220</td>
<td>0.436</td>
<td>0.504</td>
<td>0.255 to 0.993</td>
<td>.039</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Trillet-Lenoir</td>
<td>0.262</td>
<td>0.531</td>
<td>0.492</td>
<td>0.308 to 0.787</td>
<td>.002</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Zinzani</td>
<td>0.052</td>
<td>0.208</td>
<td>0.249</td>
<td>0.087 to 0.716</td>
<td>.004</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Fossa</td>
<td>0.192</td>
<td>0.295</td>
<td>0.653</td>
<td>0.420 to 1.016</td>
<td>.055</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Doorduijn</td>
<td>0.365</td>
<td>0.448</td>
<td>0.816</td>
<td>0.641 to 1.039</td>
<td>.098</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Ösby CHOP</td>
<td>0.337</td>
<td>0.500</td>
<td>0.673</td>
<td>0.482 to 0.941</td>
<td>.018</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Ösby CNOP</td>
<td>0.320</td>
<td>0.500</td>
<td>0.641</td>
<td>0.455 to 0.903</td>
<td>.009</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Timmer-Bonte</td>
<td>0.180</td>
<td>0.318</td>
<td>0.566</td>
<td>0.329 to 0.973</td>
<td>.035</td>
</tr>
<tr>
<td><strong>Combined Filgrastim</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.614</strong></td>
<td><strong>0.525 to 0.718</strong></td>
<td><strong>.000</strong></td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Gebbia</td>
<td>0.116</td>
<td>0.326</td>
<td>0.357</td>
<td>0.141 to 0.905</td>
<td>.019</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Gebbia</td>
<td>0.217</td>
<td>0.643</td>
<td>0.338</td>
<td>0.148 to 0.770</td>
<td>.002</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Chevallier</td>
<td>0.590</td>
<td>0.712</td>
<td>0.829</td>
<td>0.636 to 1.080</td>
<td>.162</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Bui</td>
<td>0.227</td>
<td>0.577</td>
<td>0.394</td>
<td>0.170 to 0.911</td>
<td>.014</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Gisselbrecht</td>
<td>0.634</td>
<td>0.775</td>
<td>0.818</td>
<td>0.668 to 1.002</td>
<td>.050</td>
</tr>
<tr>
<td><strong>Combined Lenograstim</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.623</strong></td>
<td><strong>0.442 to 0.879</strong></td>
<td><strong>.007</strong></td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Vogel</td>
<td>0.013</td>
<td>0.168</td>
<td>0.077</td>
<td>0.034 to 0.175</td>
<td>.000</td>
</tr>
<tr>
<td><strong>Combined Pegfilgrastim</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.077</strong></td>
<td><strong>0.034 to 0.175</strong></td>
<td><strong>.000</strong></td>
</tr>
<tr>
<td><strong>All G-CSF</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.538</strong></td>
<td><strong>0.430 to 0.673</strong></td>
<td><strong>.000</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
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<th>Control Rate</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Crawford</td>
<td>0.084</td>
<td>0.087</td>
<td>0.973</td>
<td>0.391 to 2.420</td>
<td>.953</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Pettengell</td>
<td>0.146</td>
<td>0.103</td>
<td>1.427</td>
<td>0.435 to 4.675</td>
<td>.554</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Trillet-Lenoir</td>
<td>0.015</td>
<td>0.047</td>
<td>0.328</td>
<td>0.035 to 3.073</td>
<td>.302</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Zinzani</td>
<td>0.000</td>
<td>0.000</td>
<td>0.936</td>
<td>0.019 to 46.556</td>
<td>.973</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Fossa</td>
<td>0.038</td>
<td>0.116</td>
<td>0.331</td>
<td>0.124 to 0.883</td>
<td>.019</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Doorduijn</td>
<td>0.056</td>
<td>0.094</td>
<td>0.596</td>
<td>0.289 to 1.228</td>
<td>.155</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Ösby CHOP</td>
<td>0.010</td>
<td>0.048</td>
<td>0.206</td>
<td>0.024 to 1.732</td>
<td>.105</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Timmer-Bonte</td>
<td>0.067</td>
<td>0.106</td>
<td>0.637</td>
<td>0.237 to 1.712</td>
<td>.366</td>
</tr>
<tr>
<td><strong>Combined Filgrastim</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.603</strong></td>
<td><strong>0.410 to 0.887</strong></td>
<td><strong>.010</strong></td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Chevallier</td>
<td>0.000</td>
<td>0.000</td>
<td>0.968</td>
<td>0.020 to 47.992</td>
<td>.987</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Bui</td>
<td>0.000</td>
<td>0.000</td>
<td>1.174</td>
<td>0.024 to 56.861</td>
<td>.935</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Gisselbrecht</td>
<td>0.037</td>
<td>0.038</td>
<td>0.976</td>
<td>0.203 to 4.691</td>
<td>.975</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Gatzeimeier</td>
<td>0.050</td>
<td>0.065</td>
<td>0.767</td>
<td>0.294 to 2.002</td>
<td>.586</td>
</tr>
<tr>
<td><strong>Combined Lenograstim</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.837</strong></td>
<td><strong>0.383 to 1.833</strong></td>
<td><strong>.657</strong></td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Vogel</td>
<td>0.011</td>
<td>0.030</td>
<td>0.359</td>
<td>0.130 to 0.988</td>
<td>.038</td>
</tr>
<tr>
<td><strong>Combined Pegfilgrastim</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.359</strong></td>
<td><strong>0.130 to 0.988</strong></td>
<td><strong>.047</strong></td>
</tr>
<tr>
<td><strong>All G-CSF</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.599</strong></td>
<td><strong>0.433 to 0.830</strong></td>
<td><strong>.002</strong></td>
</tr>
</tbody>
</table>

Secondary Prophylaxis

Secondary prophylaxis
Addition of growth factors for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received)

- Prevent that it happens again.
- Improves the ability to deliver **full dose** intensity chemotherapy and planned schedule.
<table>
<thead>
<tr>
<th>Time frame</th>
<th>FAC doses</th>
<th>Nadir counts</th>
<th>Action if &lt; ANC limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974-1986</td>
<td>400 mg d1, 8 40 mg d1 400 mg d1</td>
<td>1000/mm³</td>
<td>20% dose reduction for subsequent cycles</td>
</tr>
<tr>
<td>1986-1994 (DM86-012)</td>
<td>500 mg d1, 8 50 mg d1 500 mg d1</td>
<td>500/mL</td>
<td>20% dose reduction for subsequent cycles</td>
</tr>
<tr>
<td>1994-1998 (DM94-002)</td>
<td>500 mg d1, 4 50 mg d1 500 mg d1</td>
<td>1000/mm³</td>
<td>unknown</td>
</tr>
<tr>
<td>1998-2001 (DM98-240)</td>
<td>500 mg d1, 4 50 mg d1 500 mg d1</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>2002-2008 (ID01-580)</td>
<td>500 mg d1 100 mg d1 (epirubicin) 500 mg d1</td>
<td>N/A</td>
<td>Held if ANC ≤ 1,200/mm³ on day of tx until recovery</td>
</tr>
<tr>
<td>2012-Present (2012-0167)</td>
<td>500 mg/m² d1 50 mg/m² d1 (or epi 100mg/m²) 500 mg d1</td>
<td>N/A</td>
<td>Held if ANC ≤ 1,000/mm³ on day of tx until recovery</td>
</tr>
</tbody>
</table>

Buzdar AU et al. Cancer. 1984 Feb 1;53(3):384-9;
Green MC et al. J Clin Oncol. 2005 Sep 1;23(25):5983-92;
## ANC Thresholds with FAC/FEC

<table>
<thead>
<tr>
<th>Author, Journal, Year</th>
<th>Dose</th>
<th>Schedule</th>
<th># of cycles</th>
<th>ANC Cutoff</th>
<th>FN Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin, NEJM 2005</td>
<td>500 mg d1, 50 mg d1, 500 mg d1</td>
<td>Every 3 weeks</td>
<td>6</td>
<td>unknown</td>
<td>2.5%</td>
</tr>
<tr>
<td>Martin, NEJM 2010</td>
<td>500 mg d1, 50 mg d1, 500 mg d1</td>
<td>Every 3 weeks</td>
<td>6</td>
<td>1,500/mm³</td>
<td>2.3%</td>
</tr>
<tr>
<td>Martin, JCO 2013</td>
<td>500 mg d1, 50 mg d1, 500 mg d1</td>
<td>Every 3 weeks</td>
<td>6</td>
<td>1,500/mm³</td>
<td>3.6%</td>
</tr>
<tr>
<td>Arun, The Oncologist, 2011 (ID91-0156)</td>
<td>500 mg d1, 50 mg d1, 500 mg d1</td>
<td>Every 3 weeks</td>
<td>4</td>
<td>1,500/mm³</td>
<td>3.5%</td>
</tr>
<tr>
<td>Kelly, JCO 2012 (ID01-580)</td>
<td>500 mg d1, 100 mg d1 (epirubicin), 500 mg d1</td>
<td>Every 3 weeks</td>
<td>4</td>
<td>1,200/mm³</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Dose Delay in Clinical trials

• ANC thresholds from studies were clear and strictly adhered to
  – Clinical practice may vary
• Patients did not receive FAC or FEC chemotherapy, if ANC was less than \( \leq 1,000/\text{mm}^3 \) in any study
• Risk of FN needs to be assessed for each individual patient
ANC and Growth Factor Use

• Martin NEJM 2010 and Martin JCO 2013
  – If ANC < 1.5 x 10^9/L on day 21:
    • Hold chemotherapy
    • CBC should be repeated every two days until recovery
    • Consider addition of G-CSF with remaining cycles
    • Stop chemotherapy if ANC < 1.5 x 10^9/L on day 35

Martín M et al. N Engl J Med. 2010 Dec 2;363(23):2200-10;
The Milan Study (Bonadonna et al) Established the Importance of Chemotherapy Dose on Survival

The Milan Study: Overall Survival With Combination Adjuvant Chemotherapy: 20-Year Follow-up (N = 386)

- 20-year relapse-free survival (RFS) and overall survival (OS) were higher in patients administered ≥ 85% of the optimal dose
- 5-year RFS was lower in patients administered < 65% of the optimal dose

OS, overall survival; RFS, relapse free survival
Patient and Chemotherapy Characteristics Can Influence Dose, Duration, or RDI

• Increased age
• Chemotherapy regimen and schedule
• Body mass index/body surface area
• Practice size, setting, and geographic location
• Disease state
• Planned cycle length
• Abnormal lab values (baseline glucose and protein levels)
• Performance status (PS)¹
• Comorbidities
• Education level
• Prior chemotherapy

RDI – relative dose intensity

¹ Increased PS was associated with dose reductions.
RDI Was Reduced in Early-Stage Breast Cancer

Incidence of Dose Delays/Reductions/Reduced RDI in Early-Stage Breast Cancer

- 55.5% of patients treated with adjuvant chemotherapy for early-stage breast cancer received RDI < 85%

RDI Was Reduced in Elderly Patients

Incidence of Dose Delays/Reductions/Reduced RDI in Patients ≥ 70 years

- 51.1% of patients aged ≥ 70 years treated for lung, breast, ovarian, and colorectal cancers and lymphomas received RDI < 85%
RDI Was Reduced in Elderly Patients With Various Cancers

- Planned RDI < 85% was common in elderly patients across tumor types.
Reduced RDI Was Associated With Worse OS in Early-Stage Breast Cancer

Retrospective analysis of patients with early-stage breast cancer treated with anthracycline-based non-taxane adjuvant chemotherapy

- 10-year probability of survival without disease recurrence was 66% (95% CI, 63–70)
- 10-year probability of survival, with or without disease recurrence was 77% (95% CI, 73–80)

Chemotherapy and neutropenia

• If ANC is below 1,500 on day 1 of chemotherapy
  – Risk of FN is increased compared to > 1,500
    • 1500 – 1000: risk slightly increased
    • 1000 – 500: risk moderately increased
    • < 500: risk greatly increased
  – Difficult to assign a risk value (%) to these scenarios, since there are no published data on this question (can extrapolate from nadir counts, but may be misleading)
• ANC will drop from baseline, so starting with a deficit will increase their risk of FN
• Delaying therapy or adding GF support appears to be a safer option than treating without any changes
• Dose reduction does not seem warranted unless:
  – ANC nadir count < 250 (day 14) and
  – Other dose-limiting side effects (e.g., FN, prolonged neutropenia)
Guidelines

- American Society of Clinical Oncology (ASCO)
  - 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.

- National Comprehensive Cancer Network (NCCN)
  - Myeloid Growth Factors

- European Society for Medical Oncology (ESMO)
  - Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications

NCCN Myeloid Growth Factors. V1.2014;
PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

In addition to the risk of the chemotherapy regimen and the specific malignancy being treated, these factors need to be considered when evaluating a patient's overall risk for febrile neutropenia.

- Older patient, notably patients age ≥65 years (See NCCN Guidelines for Senior Adult Oncology; to view the most recent version of these guidelines, visit NCCN.org)
- Previous chemotherapy or radiation therapy
- Preexisting neutropenia or bone marrow involvement with tumor
- Preexisting conditions
  - Neutropenia
  - Infection/open wounds
  - Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

NCCN- Myeloid Growth Factors

EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE

RISK ASSESSMENT FOR FEBRILE NEUTROPENIA

PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA

CHEMOTHERAPY TREATMENT INTENT

CURATIVE/ADJUVANT

PROLONG SURVIVAL/QUALITY OF LIFE

SYMPTOM MANAGEMENT/QUALITY OF LIFE

CSFs (category 1 for G-CSFs)

CSFs (category 1 for G-CSFs)

CSFs

Consider CSF

Consider CSF

Consider CSFs

No CSFs

No CSFs

No CSFs

CSFs, colony-stimulating factors.

Only consider CSFs if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

The use of CSFs in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine the risk is 10% to 20%, CSFs are reasonable. However, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less-myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.
Breast Cancer Regimen Risk Evaluation

**High Risk for Febrile Neutropenia (>20%)**

- Breast Cancer
  - Docetaxel + trastuzumab (metastatic or relapsed)\(^2\)
  - Dose-dense AC followed by T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)\(^3\)
  - TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)\(^4\)

**Intermediate Risk for Febrile Neutropenia (10%-20%)**

- Breast Cancer
  - Docetaxel every 21 days\(^34\)
  - CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)\(^35\)
  - AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)\(^36\)
  - AC + sequential docetaxel + trastuzumab (adjuvant)\(^37\)
  - FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel\(^38\)
  - Paclitaxel every 21 days (metastatic or relapsed)\(^39\)

TC also added to most recent guidelines
## Incidence of Febrile Neutropenia With Select Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Breast Cancer Treatment Regimen*</th>
<th>Grade 3-4 Neutropenia</th>
<th>Febrile Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AT</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>97%</td>
<td>33%</td>
</tr>
<tr>
<td>Doxorubicin 50 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1, followed by docetaxel 75 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1. Repeat cycle q21 days up to 8 cycles (n = 213).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not reported</td>
<td>17%</td>
</tr>
<tr>
<td>Docetaxel 100 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1. Repeat cycle q21 days up to 4 cycles (n = 465).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TAC</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1, doxorubicin 50 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1, cyclophosphamide 500 mg/m&lt;sup&gt;2&lt;/sup&gt; day 1. Repeat cycle q21 days for 6 cycles (n = 744).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*G-CSF use not standardized.

Incidence of Febrile Neutropenia associated to TC

- FN rate in clinical trials 5%, but retrospective reviews indicate the rate is much higher.

<table>
<thead>
<tr>
<th></th>
<th>TC n=87</th>
<th>TC+upfront PF n=153</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>30%</td>
<td>4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>38% (3.8 days)</td>
<td>11% (2.9 days)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dose delay</td>
<td>11.0%</td>
<td>4.6%</td>
<td>0.046</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>9.2%</td>
<td>8.5%</td>
<td>NS</td>
</tr>
</tbody>
</table>

35.6% of patients without PG upfront received secondary prophylaxis.

- Seven Australian centers (300 TC-treated patients)
  - 24.2% of patients experienced FN
  - Among those with FN, 91.8% experienced it after cycle 1

Febrile neutropenia is defined as, single temperature: ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit NCCN.org).

Dose-limiting neutropenic event could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy.
Table 4. Special situations for the use of hGFs for standard therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Special situation</th>
<th>Use of hGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prophylaxis</td>
<td>Reduced marrow reserve (e.g., ANC &lt;1.5 × 10^9/l) due to radiotherapy of &gt;20% marrow, Human immunodeficiency virus, Patients aged ≥65 years treated with curative regimens (CHOP or more intensive regimens for patients with aggressive NHL)</td>
<td>Yes [III, C]</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>Further infections in the next treatment cycle considered life threatening, Dose reduction below threshold, Delay of chemotherapy, Lack of protocol adherence if compromising cure rate, overall or disease-free survival</td>
<td>Yes</td>
</tr>
<tr>
<td>Therapy of afebrile neutropenia</td>
<td>–</td>
<td>No [II, D]</td>
</tr>
<tr>
<td>Therapy of FN</td>
<td>General</td>
<td>No [C]</td>
</tr>
<tr>
<td>Therapy of high-risk FN</td>
<td>Protracted FN (&gt;7 days), hypotension, sepsis, pneumonia or fungal infection</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NHL, non-Hodgkin's lymphoma.

Growth Factor Dosing

MYELOID GROWTH FACTORS FOR PROPHYLAXIS AND TREATMENT OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim or tbo-filgrastim\(^1\) (category 1)
  > Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until postnadir ANC recovery to normal or near-normal levels by laboratory standards.
  > Start the next day up to 3-4 days after completion of chemotherapy and treat through postnadir recovery.

- Pegfilgrastim (category 1) (for prophylactic use only)
  > One dose of 6 mg per cycle of treatment.
  > Most trials administered pegfilgrastim the day after chemotherapy (category 1).
  > Administration of pegfilgrastim up to 3-4 days after chemotherapy is also reasonable based on trials with filgrastim.
  > Limited data suggest that same-day administration of pegfilgrastim may be considered in certain circumstances.\(^2\)

  > There is evidence to support use for chemotherapy regimens given every 3 wk (category 1).
  > There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 wk.
  > There are insufficient data to support use for weekly chemotherapy regimens; therefore, use of pegfilgrastim cannot be recommended.
Pegfilgrastim

- Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.
Important Safety Information

• Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta for ARDS.

• Severe sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

• Bone pain and pain in extremity occurred at a higher incidence in pegfilgrastim-treated patients as compared with placebo-treated patients.
Conclusions

• Prophylactic growth factors (i.e. pegfilgrastim) are recommended for chemotherapy regimens with a high risk for febrile neutropenia (i.e. TAC, dose-dense AC, TC).

• Prophylactic growth factors can be considered for chemotherapy regimens with an intermediate risk for febrile neutropenia.

• Patients receiving FAC chemotherapy should have an ANC greater than 1,000/mm$^3$ on the day of treatment, unless a prophylactic growth factor is administered 24 hours after chemotherapy.

• Follow national guidelines for secondary prophylaxis.
Summarizing the Need for G-CSF Support First and Every Cycle

• The risk of febrile neutropenia in patients with breast cancer is significant.
• Febrile neutropenia is a risk through all cycles of chemotherapy.
• Continued use of G-CSF prophylaxis during all cycles of chemotherapy is of clinical relevance.
• Breast cancer patients with febrile neutropenia typically require hospitalization.
• In a retrospective analysis of patients receiving TAC chemotherapy, only 75% received primary G-CSF prophylaxis first and every cycle.
• Primary prophylaxis with pegfilgrastim has been shown to result in a 94% reduction in the incidence of febrile neutropenia.
• National guidelines recommend risk assessment of all patients receiving myelosuppressive chemotherapy, with primary G-CSF prophylaxis for all patients at high risk of developing febrile neutropenia.