SAFETY and EFFICACY of CHEMOTHERAPY: key contributions of proper G-CSF usage in solid tumours

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(Japanese Association for Supportive Care)
DISCLOSURE OF INTEREST

Dr. Matti Aapro

Consultant to
Accord, Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor

and has received honoraria for lectures at symposia of
Accord, Amgen, Bayer Schering, Biocon, Boehringer, Cephalon, Chugai, Eisai, DrReed, Genomic Health, Glenmark, GSK, Helsinn, Hospira, Ipsen, JnJ, OrthoBiotech, Kirin Kyowa, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor
Myeloid Growth Factors for Chemotherapy-Associated Neutropenia

Myelosuppressive chemotherapy

<500 neutrophils

Febrile neutropenia (FN)

Complicated life-threatening infection and prolonged hospitalisation

Reduced survival

Chemotherapy dose delays and dose reductions

Decreased relative dose intensity (RDI)

References:
**FN Is a Serious Complication**

*Solid and Nonsolid Tumours: Increased Risk of Death*

- In an exploratory analysis that allowed for the occurrence of FN at any time during the entire study period, the unadjusted results showed significant differences in survival.

- The adjusted HR for FN on overall mortality was 1.53 (95% CI, 1.35-1.72) and on early mortality was 1.54 (95% CI, 1.29-1.85).

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Overall Mortality Incidence per 1000 Person-Months (95% CI)</th>
<th>Early Mortality Incidence per 1000 Person-Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with FN</td>
<td>Patients without FN</td>
</tr>
<tr>
<td>Breast</td>
<td>2.9 (2.5-3.4)</td>
<td>2.3 (1.9-2.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>44.3 (39.6-49.6)</td>
<td>29.6 (26.0-33.8)</td>
</tr>
<tr>
<td>NHL</td>
<td>7.2 (5.3-9.7)</td>
<td>3.3 (2.1-5.1)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>8.4 (7.1-9.9)</td>
<td>6.4 (5.3-7.8)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>5.6 (3.9-8.2)</td>
<td>4.4 (2.9-6.7)</td>
</tr>
<tr>
<td>All tumour types</td>
<td>7.9 (7.3-8.5)</td>
<td>5.6 (5.1-6.1)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin lymphoma.
Clinical Consequences of Neutropenia and FN

- Reduced RDI resulted in lower OS in patients with ESBC receiving anthracycline-containing chemotherapy\(^1\)
- Reduced RDI resulted in lower OS in patients with DLBCL receiving CHOP-21 chemotherapy\(^2\)

ARDI, average relative dose intensity; CHOP-21, cyclophosphamide-doxorubicin-vincristine-prednisone given every 3 weeks; DLBCL, diffuse large B-cell lymphoma; ESBC, early stage breast cancer; OS, overall survival.

Increasing the dose intensity of adjuvant chemotherapy: an EBCTCG meta-analysis

Richard Gray, Rosie Bradley, Jeremy Braybrooke, Christina Davies, Hongchao Pan, Richard Peto, Judith Bliss, David Cameron, John Mackey, Lucia Del Mastro, Sandra Swain, Michael Untch, Jonas Bergh, Kathleen Pritchard, Larry Norton, for the

Early Breast Cancer Trialists’ Collaborative Group

All authors declare no relevant conflict of interest
Guidelines
Once upon a time, there was....

SPECIAL ARTICLE

American Society of Clinical Oncology Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines

Adopted on September 13, 1994, by the American Society of Clinical Oncology

Purpose: Standard practice in protecting against chemotherapy-associated infection has been chemotherapy dose modification or dose delay, administration of progenitor-cell support, or selective use of prophylactic antibiotics. Therapy of chemotherapy-associated neutropenic fever or infection has customarily involved treatment with intravenous antibiotics, usually accompanied by hospitalization. The hematopoietic colony-stimulating factors (CSFs) have been introduced into clinical practice as additional supportive measures that can reduce the likelihood of neutropenic complications due to chemotherapy. Clinical benefit has been shown, but the high cost of CSFs has led to concern about their appro-

available, the Panel placed greatest value on survival benefit, reduction in rates of febrile neutropenia, decreased hospitalization, and reduced costs. Lesser value was placed on alterations in absolute neutrophil counts (ANC).

Conclusions: CSFs are recommended in some situations, eg, to reduce the likelihood of febrile neutropenia when the expected incidence is ≥ 40%; after documented febrile neutropenia in a prior chemotherapy cycle to avoid infectious complications and maintain dose-intensity in subsequent treatment cycles when chemotherapy dose-reduction is not appropriate; and after high-dose chemotherapy with autologous progenitor-cell trans-
Guidelines for the use of G-CSF


Courtesy Prof K. Tamura
Prof Jordan invites you:
Visit us: www.s3supportiv.de
Our promise: pure German science language - very easy to understand!
586 pages, excluding method report
Patient assessment algorithm to decide if primary prophylactic G-CSF usage is warranted

Step 1
Assess frequency of FN associated with the planned chemotherapy regimen

- FN risk ≥20%
- FN risk 10%-20%
- FN risk <10%

Step 2
Assess factors that increase the frequency/risk of FN

<table>
<thead>
<tr>
<th>High risk</th>
<th>Age &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>(level I and II</td>
<td>History of prior FN</td>
</tr>
<tr>
<td>evidence)</td>
<td>No antibiotic prophylaxis, no G-CSF use</td>
</tr>
<tr>
<td>Other factors</td>
<td>Poor performance and/or nutritional status</td>
</tr>
<tr>
<td>(level III and IV</td>
<td>Female gender</td>
</tr>
<tr>
<td>evidence)</td>
<td>Haemoglobin &lt;12 g/dL</td>
</tr>
<tr>
<td></td>
<td>Liver, renal, or cardiovascular disease</td>
</tr>
</tbody>
</table>

Step 3
Define the patient’s overall FN risk for planned chemotherapy regimen

- Overall FN risk ≥20%
- Overall FN risk <20%

Secondary prophylaxis: Start G-CSF if a neutropenic event was observed in the previous cycle

Antibiotics are NOT to be used instead or with G-CSF, except in special circumstances

- In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as a supportive treatment
  
  **Recommendation grade: A**

- If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment or when the treatment intent is to prolong survival
  
  **Recommendation grade: A**

- Where treatment intent is palliative, use of less-myelosuppressive chemotherapy or dose/schedule modification should be considered
  
  **Recommendation grade: B**
Over- and under-prophylaxis for chemotherapy-induced (febrile) neutropenia relative to evidence-based guidelines is associated with differences in outcomes: findings from the MONITOR-GCSF study

Carsten Bokemeyer¹ · Pere Gascón² · Matti Aapro³ · Heinz Ludwig⁴ · Mario Boccadoro⁵ · Kris Denhaerynck⁶,⁷ · Michael Gorray⁸ · Andriy Krendykov⁸ · Ivo Abraham⁶,⁹ ▪ Karen MacDonald⁶

<table>
<thead>
<tr>
<th></th>
<th>Under 251 (17.4%)</th>
<th>Correct 817 (56.6%)</th>
<th>Over 376 (26.0%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotoxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>0.0%</td>
<td>2.1%</td>
<td>36.4%</td>
<td></td>
</tr>
<tr>
<td>10–20%</td>
<td>46.6%</td>
<td>36.0%</td>
<td>63.6%</td>
<td></td>
</tr>
<tr>
<td>≥20%</td>
<td>53.4%</td>
<td>61.9%</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

⁵ Stage 4 (stage 3 if multiple myeloma) and prior chemotherapy in metastatic setting n.s. not significant
Primary Granulocyte Colony-Stimulating Factor Prophylaxis During the First 2 Cycles Only or Throughout All Chemotherapy Cycles in Patients with Breast Cancer at Risk for Febrile Neutropenia

Incidence of febrile neutropenia per treatment arm

- **throughout**
- **first 2 cycles only**
5. Treatment with G-CSF for patients with solid tumours and malignant lymphoma and ongoing FN is indicated only in special situations.

- These are limited to patients who do not respond to appropriate antibiotic management and who are developing life-threatening infectious complications, such as severe sepsis or septic shock

_Recommendation grade: B_

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Mostly Same Recommendation 5 in 2006

**Addition was:** “Treatment with G-CSF for patients with solid tumours and malignant lymphoma and ongoing FN is indicated in special situations.”

6. WHICH G-Choice of formulation

Filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents, according to current administration guidelines, to prevent FN and FN-related complications, where indicated.

Filgrastim and pegfilgrastim biosimilars are now also a treatment option in Europe.

Recommendation grade: A.

clinical practice guidelines

Management of febrile neutropenia: ESMO Clinical Practice Guidelines†

J. Klastersky¹, J. de Naurois², K. Rolston³, B. Rapoport⁴, G. Maschmeyer⁵, M. Aapro⁶ & J. Herrstedt⁷ on behalf of the ESMO Guidelines Committee*

¹Institut Jules Bordet—Centre des Tumeurs de l'ULB, Brussels, Belgium; ²St Luke’s Cancer Centre, Royal Surrey County Hospital, Guildford, UK; ³M.D. Anderson Cancer Center, Houston, TX, USA; ⁴Medical Oncology Centre of Rosebank, Johannesburg, South Africa; ⁵Department of Hematology, Oncology and Palliative Care, Ernst von Bergmann Hospital, Potsdam, Germany; ⁶Multidisciplinary Institute of Oncology, Clinique de Genolier, Genolier, Switzerland; ⁷Department of Oncology, Odense University Hospital (OUH), Odense, Denmark
ESMO 2017 FN Management

- FN can be a serious event...
- Hospitalisation depends on...
- Antibiotic choice depends on...
ESMO 2017 FN Management

- FN can be a serious event...

The first administration of therapy should be given in the hospital within 1 h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

- Hospitalisation depends on...

- Antibiotic choice depends on...
ESMO 2017 FN Management

- FN can be a serious event...

> The first administration of therapy should be given in the hospital within 1 h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

- Hospitalisation depends on...

- Antibiotic choice depends on...
Score derived from the logistic equation of the MASCC predictive model (1386 patients with FN)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burden of illness</strong></td>
<td></td>
</tr>
<tr>
<td>▪ No or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>▪ Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no previous fungal infection in hematological ca</td>
<td>4</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

Threshold: score ≥ 21 (maximum 26) predicting less than 5% of severe complications

ESMO 2017 FN Management

- FN can be a serious event...
  
  The first administration of therapy should be given in the hospital within 1 h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

- Hospitalisation depends on...
  - ....MASCC Score

- Antibiotic choice depends on...
ESMO 2017 FN Management

- FN can be a serious event...

  The first administration of therapy should be given in the hospital within 1 h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

- Hospitalisation depends on...
  - ....MASCC Score

- Antibiotic choice depends on...

As already mentioned, the spectrum of infection in cancer patients is different from place to place and changes over time; therefore, paying attention to local epidemiology is crucial [14].

ESMO 2017 FN Management

- FN can be a serious event...

> The first administration of therapy should be given in the hospital within 1 h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

- Hospitalisation depends on...MASCC Score

- Antibiotic of choice is ...

As already mentioned, the spectrum of infection in cancer patients is different from place to place and changes over time; therefore, paying attention to local epidemiology is crucial [14].

ESMO 2017 FN Management

- FN can be a serious event...

  The first administration of therapy should be given in the hospital within 1 h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

- Hospitalisation depends on...MASCC Score

- Antibiotic of choice is ...

  Or oral fluoroquinolone and amoxicillin/clavulanate (or clindamycin if allergy) in non pretreated patients

REVISION OF ESMO GUIDELINES

- Will comprise of the discussed points
- Will address weekly chemotherapy and the lack of evidence
- Will address the different patterns of neutropenia related to CDK4/6 inhibitors and immunotherapy
- Will rediscuss longer and shorted acting
- And much more...
thank you