Febrile Neutropenia – Guidelines Update and Approach to Management of Both High- and Intermediate-Risk Patients

Bernardo Rapoport

The Medical Oncology Centre of Rosebank, Johannesburg
and
Department of Immunology, Faculty of Health Sciences, University of Pretoria

SOUTH AFRICA
<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/ Expenses</th>
<th>Consulting/ Advisory Board</th>
<th>Contract Research</th>
<th>Funded Research</th>
<th>Royalties/ Patent</th>
<th>Stock Options</th>
<th>Ownership/ Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck &amp; Co., Inc</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Roche</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Sandoz</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Tesaro</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Teva</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Heron Therapeutics</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>BMS South Africa</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Novartis South Africa</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Amgem South Africa</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Bayer South Africa</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Merck Serono S.Africa</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Astellas South Africa</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Sanofi Aventis S. Africa</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Astra Zeneca S. Africa</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speakers’ bureau</td>
</tr>
<tr>
<td>Eli-Lilly South Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Introduction

- Despite major advances in prevention and treatment, FN remains one of the most frequent and serious complications of cancer chemotherapy

- Major cause of morbidity, healthcare resource use

- Compromised treatment efficacy resulting from delays and dose reductions of cancer chemotherapy

- Mortality from FN has diminished steadily, but remains significant
The risk of infection increases with the severity and duration of neutropenia

G.P. Bodey, Ann Int Med, 1966
Complications of Myelosuppressive Cancer Chemotherapy

Myelosuppressive chemotherapy

Short-term effects
- Febrile neutropenia (FN)
  - Complicated life-threatening infection and prolonged hospitalization

Long-term effects
- Chemotherapy dose delays and dose reductions
  - Decreased relative dose intensity (RDI)

Reduced survival

Kuderer NM et al. Cancer 2006;106:2258–2266
Chirivella I et al. J Clin Oncol 2006;24;abstract 668
There is a clear relationship between the severity of neutropenia (which directly influences the incidence of FN) and the intensity of chemotherapy.

Currently, the different regimens are classified:

- High risk (>20%)
- Intermediate risk (10%–20%)
- Low risk (<10%) of FN
FN Risk of >20%

- Lymphoma
  - R-ICE
- Adjuvant breast
  - FEC 100
- Adjuvant breast
  - FEC 100 T
- Neo-adjuvant or Adjuvant breast
  - TAC
- Burkitts Lymphoma
  - R-CODOX-M
- Bladder
  - MVAC
- Sarcoma
  - MAID
- Sarcoma
  - Doxorubicin-ifosfamide
- Small-cell lung cancer
  - CAE
- Testicular cancer
  - VIP
More than half of the FN episodes occur in the first cycle of chemotherapy.

Bar chart showing:
- Breast cancer: 58%
- NSCLC: 50%
- SCLC: 71%
- Colon cancer: 80%
- Non-Hodgkin’s lymphoma: 53%
- Hodgkin disease: 57%
- Ovarian cancer: 54%

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer

Primary Prophylaxis with a CSF

- Starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia on basis of patient-, disease-, and treatment-related factors.

- Primary CSF the prophylaxis should also be given in patients receiving dose-dense chemotherapy when considered appropriate.
FN Risk of 10-20%
ESMO Guidelines
Age and co-morbidities

- Age plays a major role in the risk of FN and its complications

- Older patients have a higher risk of FN following chemotherapy

- Older patients have the worse morbidity and mortality rates

- Risk of FN and its complications increases when one or several co-morbidities are present in the patient
FN Prophylaxis

- FN can be effectively prevented by the use of G-CSFs
- It is recommended to use G-CSF’s in patients receiving chemotherapies with a 10-20% risk of developing FN
- Serious co-morbidities and/or aged >60 years
- Dose reduction deemed detrimental to outcome
CSF for patients with diffuse aggressive lymphoma age 65 years and older

Prophylactic G-CSF for patients with diffuse aggressive lymphoma age 65 years and older treated with curative chemotherapy (CHOP-R) should be considered, particularly in the presence of comorbidities.
Multiple Chronic Conditions

• In the case of FN, observational studies have provided important information about the impact of comorbidity.

• A 2014 systematic review reported that the presence of comorbid conditions increased the risk of FN among patients with cancer treated with chemotherapy.

• Compared with patients with no comorbid conditions, patients with three or more comorbid conditions had an 81% increased risk of FN.

• The presence of renal, hepatic, and cardiovascular disease have each been associated with FN or FN–related hospitalization.
ESMO Guidelines Neutropenia Risk
Other Risk Factors

- Advanced disease
- History of prior FN
- No antibiotic prophylaxis or G-CSF use
- Mucositis
- Poor PS
- Cardiovascular disease
Secondary Prophylaxis with G-CSFs

- Is recommended for patients who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received)

- A reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome

- In many clinical situations, dose reduction or delay may be a reasonable alternative
G-CSFs in Afebrile Patients
Guideline Recommendations

G-CSFs should not be routinely used for patients with neutropenia who are afebrile.

G-CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with uncomplicated fever and neutropenia.
High Risk for Infection-Associated Complications

G-CSFs should be considered in patients with FN

- Prognostic factors that are predictive of poor clinical outcomes
- High-risk features include expected prolonged (> 10 days)
- Profound neutropenia (< 0.1 x 10^9/L)
- Age older than 65 years
- Uncontrolled primary disease
- Pneumonia
- Hypotension and multiorgan dysfunction (sepsis syndrome)
- Invasive fungal infection
- Being hospitalized at the time of the development of fever
MASCC Index

- Multinational Association for Supportive Care in Cancer
- Prospectively validated tool to rapidly assess risk before access to neutrophil count
- Scores $\geq 21$ are at low risk of complications MASCC scoring index:
  - Burden of illness: no or mild symptoms 5
  - Burden of illness: moderate symptoms 3
  - Burden of illness: severe symptoms 0
  - No hypotension (systolic BP $>90$ mmHg) 5
  - No chronic obstructive pulmonary disease 4
  - Solid tumour/lymphoma with no previous fungal infection 4
  - No dehydration 3
  - Outpatient status at onset of fever 3
  - Age $<60$ years (not valid in children $<18$ years) 2

MASCC Score=26
Chemoprophylaxis

- Antimicrobials have been used for a long time for the prevention of episodes of FN in chemotherapy treated patients
- This approach has been somewhat successful
  - Led to the emergence of resistant strains
  - Limiting its efficacy
Chemoprophylaxis

• Guidelines from the EORTC & ASCO recommend that clinicians limit the use of antibacterial prophylaxis to patients at high risk for FN.

• Cochrane meta-analysis still recommended the use of ciprofloxacin or levofloxacin in cancer patients undergoing intensive chemotherapy.

• Others recommend avoidance.

• Fluoroquinolones, should be discouraged.
Several meta-analyses indicate that primary G-CSF prophylaxis (administered after cycle 1) reduces the FN risk by at least 50% in solid tumors patients

Guidelines recommend G-CSF be administered prophylactically if the risk of FN is >20%

FN intermediate risk (10%–20%) consider the age, coexisting morbidities, other risk factors
ESMO Guidelines

FN in high-risk situations

- Autologous stem-cell transplant  Common
- Allogeneic stem-cell transplant  Common
- During graft failure  Common
- AML at DX  35%–48%
- ALL during ALL induction  30%
ESMO Guidelines FN-related mortality in high-risk situations

- Autologous transplant: 0%–10%
- Allogeneic transplant: highly variable
- ALL during induction: 2%–10%
- AML during the first 2 months: 20%–26%
- Graft failure: 80%
ESMO Guidelines
G-CSF high-risk situations

- Autologous transplant: Yes
- Allogeneic transplant: Yes
- Graft failure: Yes
- AML: No
- MDS: No
- ALL: Controversial
The Update Committee did not provide recommendations regarding the use of G-CSFs in adults with acute myeloid leukemia or myelodysplastic syndromes.
FN Management
ESMO Clinical Practice Guidelines

Adapted from European Organisation for Research and Treatment of Cancer guidelines. FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor
**Evaluation Prior to the First Cycle of Chemotherapy**

### Evaluation Prior to First Chemotherapy Cycle

<table>
<thead>
<tr>
<th>RISK ASSESSMENT FOR FEBRILE NEUTROPENIA</th>
<th>PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE</td>
<td>CURATIVE/ADJUVANT</td>
</tr>
<tr>
<td>Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignancies</td>
<td>High (&gt;20%)</td>
</tr>
<tr>
<td>Intermediate (10%-20%)</td>
<td>Consider CSF</td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>No CSFs</td>
</tr>
</tbody>
</table>

CSFs = Colony-stimulating factors; G-CSFs = Granulocyte colony-stimulating factors

---

*See Evaluation Prior to Second and Subsequent Chemotherapy Cycles (MGF-2)*
G-CSF and pegfilgrastim dose schedule, route of application

- Pegfilgrastim at a total dose of 6 mg
- Equivalent dose of filgrastim is 5 μg/kg/day for ~10 days
- EMA/FDA approved biosimilars can be considered
G-CSF Side Effects

- Bone Pain 25%
- Pain in the extremities 5-10%
G-CSF Side Effects

- Allergic reactions
  - Skin: rash, urticaria, facial edema
  - Respiratory: wheezing, dyspnea
  - Cardiovascular: hypotension, tachycardia, anaphylaxis
- Bleomycin-containing regimens: pulmonary toxicity
- Splenic rupture
- Acute respiratory distress syndrome
- Alveolar hemorrhage and hemoptyisis
- Sickle cell crises (only in patients with sickle cell disease)
- MDS and AML

- Precautions
  - Cutaneous vasculitis
  - Immunogenicity
Primary prophylaxis with G-CSF is not indicated during chemoradiotherapy to the chest due to the increased rate of bone marrow suppression associated with an increased risk of complications and death.

There is also a risk of worsening thrombocytopenia when G-CGFs are given immediately before or simultaneously with chemotherapy.
## Conclusion

<table>
<thead>
<tr>
<th>FN risk</th>
<th>ESMO</th>
<th>ASCO</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to high (&gt; 20 %)</td>
<td>Use G-CSFs</td>
<td>Use G-CSFs</td>
<td>Use G-CSFs</td>
</tr>
<tr>
<td>Intermediate (10-20 %)</td>
<td>Consider</td>
<td>Consider</td>
<td>Consider</td>
</tr>
<tr>
<td>Consider other risk factors</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Low (&lt; 10 %)</td>
<td>Not specified</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
Conclusion
Take home message

1. Myelosuppressive chemotherapy is associated with severe morbidity and mortality

2. ESMO Guidelines (ASCO & NCCN) recommends the usage G-CSF to prevent FN and serious infective complications associated with chemotherapy

3. Clinical evaluation of patients risk factors with every cycle of chemotherapy is imperative
Thank You
Questions?