Implications of neutropenia in elderly patients

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Disclosures

- Honoraria from Chugai, Roche, Vifor.
Outline

- Impact of aging on granulopoiesis
- Consequences of neutropenia
- Therapeutic implications: G-CSF
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- Impact of aging on granulopoiesis
- Consequences of neutropenia
- Therapeutic implications: G-CSF
**Stem cells hallmarks**

- Symmetric and asymmetric cell divisions
  - Response to injury
  - Regeneration

- Morrison, Nature 2012
A stem cell theory of aging and cancer

Stem cells are regulated during aging:
– Cell autonomous pathways
– Cell nonautonomous pathways: a central function of the environment (niche)

Telomere dysfunction induces environmental alterations limiting hematopoietic stem cell function and engraftment

Zhenyu Ju¹, Hong Jiang¹, Maike Jaworski², Chozhavendan Rathinam³, Anne Gompe¹, Christoph Klein³, Andreas Trumpp² & K Lenhard Rudolph¹

Ju et al. Nature Medicine, 2007
Consequences of aging on white lineage

- In old mice, stem cells have a p16\textsuperscript{INK4a}-dependant decreased ability of self-renewal, bone marrow addressing and a myeloid skewing.

Bone marrow exhaustion is revealed by chemotherapy

Baseline and early lymphopenia predict for the risk of febrile neutropenia after chemotherapy.


Ray-Coquard, BrJCancer 2003
Outline

- Impact of aging on granulopoiesis
- Consequences of neutropenia
- Therapeutic implications: G-CSF
Consequences of neutropenia

Febrile neutropenia (FN)
- Mortality: 9.5%
- Median hospital stay: 11.5 days
- Infection risk correlated to:
  - Neutropenia duration
  - Number of comorbidities

Kuderer, Cancer 2006
Crawford, J. Cancer 2004
Lyman, Crit Rev Oncol Hematol 2014
Outline

- Impact of aging on granulopoiesis
- Consequences of neutropenia
- Therapeutic implications: G-CSF
Which growth factors?

- Recombinant GM-CSF:
  - SARGROMOSTIM LEUKINE® (r-HuGM-CSF)
- Recombinant G-CSF:
  - LENOGRASTIM GRANOCYTE® (r-metHuG-CSF)
  - FILGRASTIM NEUPOGEN® (r-metHuG-CSF)
  - PEGFILGRASTIM NEULASTA®
Preclinical data

- **G-CSF**: 
  - Proliferation and differentiation of myeloid progenitors
  - Increase of phagocytosis, of antibodies-dependant cytotoxicity, of superoxydes release

- **GM-CSF**: 
  - Proliferation and differentiation of myeloid progenitors, monocytes/macrophages, dendritic cells
  - *in vitro et in vivo* action on other lineages
Indications

- **G-CSF**
  - Reduce duration of neutropenia and the occurrence of febrile neutropenia in patients receiving chemotherapy that is cytotoxic (excepted chronic myeloid leukemia and myelodyplasia).
  - **Reduce the duration of neutropenia in patients underdoing treatment to destroy the bone marrow cells before a bone marrow transplant**, if they have a risk of long-term, severe neutropenia.
  - **Mobilization of progenitor cells in peripheral blood.**
  - **Severe congenital, cyclic or idiopathic neutropenia** with neutrophils count less than 0.5 x 10^9/l and history of severe or repeated infections.
  - **Treat persistent neutropenia in patients with advanced human-immunodeficiency-virus (HIV) infection**, to reduce the risk of bacterial infections when other treatments are not appropriate.
Meta-analyses

- 148 trials (16838 pts 8474 +G-CSF, 8365 wo)  
  - Early mortality: NS  
  - Infection-related deaths: NS  
  - Documented infections (paraclinics) 38,9% vs 43,1%, RR 0,85 [0,79-0,92]  
  - Documented infections (bacteriology) 23,5% vs 28,6%, RR 0,86 [0,77-0,96]  
  - Febrile neutropenia events 25,3% vs 44,2%, RR 0,71 [0,63-0,80]  

- 17 trials (3493 pts)  
  - Infection-related mortality, RR 0.55 [0.33-0.90], p=0.018  
  - Early mortality RR 0.60 [0.43 to 0.83], p=0.002  
  - Febrile neutropenia events RR 0.54 [0.43-0.67], p=0.001  

- 61 trials (4251 pts + G-CSF, 5188 wo)  
  - All causes of mortality RR 0.93 [0.90-0.96], P < 0.001
Recommandations

- EORTC 2010

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<table>
<thead>
<tr>
<th>Malignancy</th>
<th>FN risk category (%)</th>
<th>Chemotherapy regimen and reference</th>
<th>FN risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>&gt;20</td>
<td>AC → docetaxel^{19,54,55} Paclitaxel → AC^{54} Doxorubicin/docetaxel^{56,57} Doxorubicin/paclitaxel^{19,45,58} TAC^{19,59,60} DD/DDG FEC^{61}</td>
<td>5–25</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>&gt;20</td>
<td>ACE^{6,19,47,75–78} Topotecan^{19,79} Topotecan/paclitaxel^{19} ICE^{80} VICE^{81}</td>
<td>24–57</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>&gt;20</td>
<td>Docetaxel/carboplatin^{19,44} Etoposide/cisplatin^{86} VIG^{19,87}</td>
<td>26, 54</td>
</tr>
<tr>
<td>Non-Hodgkins lymphoma</td>
<td>&gt;20</td>
<td>DHAP^{19,96} ESHAP^{19,97–99} CHOP-21^{4,100} DD/DDG^{c} VAPEC-B^{19,101} DD/DDG^{c} ACVB^{19,102}</td>
<td>48, 17–50</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>&gt;20</td>
<td>Docetaxel^{19,105} Paclitaxel^{19,106}</td>
<td>33, 22</td>
</tr>
<tr>
<td>Urothelial cancer</td>
<td>&gt;20</td>
<td>Paclitaxel/carboplatin^{113} MVAC^{114} DDG^{c} MVAC^{114}</td>
<td>25, 26</td>
</tr>
<tr>
<td>Germ cell tumours</td>
<td>&gt;20</td>
<td>BOP → VIP-B^{46} VeIP^{19,115}</td>
<td>46, 67</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>&gt;20</td>
<td>TIC (head and neck cancers)^{19,126} MAID (sarcoma)^{19,127} Paclitaxel/cisplatin (cervical cancer)^{19,128}</td>
<td>30, 58</td>
</tr>
</tbody>
</table>

Aapro, EJC 2006
Secondary events (1)

**Certain:**
- Bone pain (20% vs 10%)
- Fever
- Injection-site pain

**Hypothetical**
- «(in) 531 SCN patients with an average follow-up of 4.0 years (...), the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. (...) the cumulative risk of developing leukemia or MDS by the end of the 8th year of NEUPOGEN® treatment in a patient with congenital neutropenia was 16.5% (95% C.I. = 9.8%, 23.3%); this represents an annual rate of approximately 2%. It is also unknown if the rate of conversion in patients who have not received NEUPOGEN® is different from that of patients who have received NEUPOGEN®.
- But...

The long-term effects of long-acting growth factors are unknown, and the Update Committee expressed concern about potential leukocytosis, late neutropenia after discontinuation of pegylated G-CSF, and the need for long-term safety data.
Secondary events (2)

- Hypothetical
  - Anaemia
    
    Does Granulocyte Colony-Stimulating Factor Worsen Anemia in Early Breast Cancer Patients Treated With Epirubicin and Cyclophosphamide?
    
    Papaldo, JCO 2006

  - Thrombopenia
  - Leucocytosis
    
    Myeloid Toxicity in Breast Cancer Patients Receiving Adjuvant Chemotherapy With Pegfilgrastim Support
    
    Wolff, JCO 2006
Administration modalities (1)

- Initially
  - J2-J15
  - ASCO 2006: 24 to 72 hours after chemotherapy, until leucocytes > 2-3 G/l
  - Different schedules comparison
    - 480 µg/j ou 300 µg/j J8 à J14
    - 480 µg/j ou 300 µg/j J8, J10, J12, J14
    - 300 µg/j J8 & J14

- Conclusion: 300 µg/j J8 & J14 schedule feasible, less bone pain, less fever events
- Critics: EC (120mg/m², 600mg/m²): FN rate 7%, under-powered trial

Impact of Five Prophylactic Filgrastim Schedules on Hematologic Toxicity in Early Breast Cancer Patients Treated With Epirubicin and Cyclophosphamide

Papaldo, JCO 2005
### French surveys 1999 et 2006-2007


<table>
<thead>
<tr>
<th>Date of first injection</th>
<th>1999</th>
<th>2006-2007</th>
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<tbody>
<tr>
<td></td>
<td>All (n=817)</td>
<td>All (n=923)</td>
</tr>
<tr>
<td></td>
<td>Lenograstim</td>
<td>Filgrastim</td>
</tr>
<tr>
<td></td>
<td>Pegfilgrastim</td>
<td></td>
</tr>
<tr>
<td>Before / during</td>
<td>136 (16.6%)</td>
<td>124 (13.4%)</td>
</tr>
<tr>
<td>chemotherapy</td>
<td>54 (15.3%)</td>
<td>32 (17.6%)</td>
</tr>
<tr>
<td></td>
<td>37 (9.6%)</td>
<td></td>
</tr>
<tr>
<td>From J+1 to J+3</td>
<td>273 (33.4%)</td>
<td>606 (65.7%)</td>
</tr>
<tr>
<td></td>
<td>198 (55.9%)</td>
<td>77 (42.3%)</td>
</tr>
<tr>
<td></td>
<td>332 (85.8%)</td>
<td></td>
</tr>
<tr>
<td>J+4 and after</td>
<td>408 (49.9%)</td>
<td>193 (20.9%)</td>
</tr>
<tr>
<td></td>
<td>102 (28.8%)</td>
<td>73 (40.1%)</td>
</tr>
<tr>
<td></td>
<td>18 (4.7%)</td>
<td></td>
</tr>
</tbody>
</table>

#### 2011 : 791 pts
- Before/during chemotherapy: 3%

*Falandry, Eur J Cancer 2010*

*Falandry, Anticancer Res 2014*
Use of G-CSF during chemotherapy?
- GM-CSF priming could reduce myelosuppression
- G-CSF priming: worsens myelosuppression
Practice analyses

**USA:**
Great variability depending on: health insurance, individual medical practices

**France**
Age ++
An impact of targeted therapies?

- **Bevacizumab**
  - Lung – ECOG
  - Carbo-Taxol-Bevacizumab (434) vs Carbo-Taxol (444)
  - Grade 3-4 neutropenias: 25.5% vs 16%

- **Cetuximab**
  - Poumon – FLEX
  - Cisplatine-Navelbine-Cetuximab vs Cisplatine-Navelbine
  - FN : 22% vs 15%

*Rosell, Ann Oncol 2008*
*Sandler, NEJM 2006*
Conclusions

- Age induces in hematopoietic stem cells:
  - decreased ability of self-renewal, bone marrow addressing
  - a myeloid skewing
  - A higher turn-over of myeloid lineages
  - Bone marrow exhaustion is revealed by chemotherapy

- Concerning neutropenia and G-CSF:
  - Some certainties
    - Decrease incidence and duration of neutropenic events
    - Improves survival
  - Some questions and controversies
    - Immediate myelotoxicity
    - ... and long myelotoxicity
    - Administration schedules
Age induces defects in hematopoiesis that are revealed during chemotherapy.

G-CSG in the elderly use should follow international guidelines:
- Certainty: increased risk associated with neutropenic events in the elderly.
- Controversy: impact of G-CSF in bone marrow aging?