Overview of Use of G-CSF in the Treatment of Acute Radiation Injury

Glen Reeves

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Outline of Presentation

- Pharmacodynamics of granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF, GM-CSF)
- Clinical usage in treatment of accident victims (selected cases)
- Current consensus guidelines for CSF usage
- Summary
Pharmacodynamics

- Stimulate marrow recovery of granulocytes and macrophages by accelerating maturation process and delaying neutrophil decline (in radiotherapy and chemotherapy patients)
- Accelerates proliferation and differentiation
- Counteracts apoptosis in CNS neurons and induces neurogenesis
- Rapid renal excretion (unless pegylated)
- Normal product of macrophages, endothelial tissue, other immune tissues
Pharmacodynamics (cont.)

- Transient effects: myalgias, fever, local reaction
- Major side effects: splenomegaly, ARDS, sickle cell crisis
- Can induce terminal differentiation in myeloid leukemia cell lines
Granulocyte-Macrophage CSF

• Stimulates monocytes as well as granulocytes
  • Monocytes become dendritic cells as well as macrophage
• Similar mechanisms to G-CSF
• GM-CSF overproduced in rheumatoid arthritis
Clinical Usage—Planned Treatment

- Reduces risk of febrile neutropenia in adults receiving chemotherapy, regardless of type
  - Fewer deaths during chemotherapy
  - Fewer deaths from infection
  - Shorter recovery time for neutrophils after cytoreduction
  - More likely to complete chemotherapy regimen
## CSF Use in Radiation Accidents

<table>
<thead>
<tr>
<th>Place, Year</th>
<th>Source; Exposure</th>
<th>Dose (TBI)</th>
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<tbody>
<tr>
<td>Goiânia, 1987</td>
<td>Cs-137; protracted (14 days)</td>
<td>2.5 – 6.0 gray</td>
<td>8 (7 were evaluable)</td>
<td>GM-CSF 500 µg/m² 24-48 days duration</td>
<td>4/8 survive 2-6 days to respond Rebound drop</td>
</tr>
<tr>
<td>San Salvador, 1989</td>
<td>Co-60; acute</td>
<td>8.2 in 1; 3-3.8 Gy in 2</td>
<td>3</td>
<td>GM-CSF 240 µg/m²</td>
<td>TNC increased to 1500/µL in 20, 10, &amp; 9 days</td>
</tr>
<tr>
<td>Soreq, Israel, 1990</td>
<td>Co-60; acute</td>
<td>10-20 Gy</td>
<td>1</td>
<td>GM-CSF 250 µg/m² day 1-18</td>
<td>Engrafted BMT. Died D+36; GVH?</td>
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<td>Nesvizh, Belarus, 1992</td>
<td>Co-60; acute</td>
<td>11 Gy (12-15 some estimates)</td>
<td>1</td>
<td>GM-CSF 200-600 μg/m² day 3-40</td>
<td>Marrow recovery. Died D+108</td>
</tr>
<tr>
<td>Gilan, Iran, 1996</td>
<td>Ir-192; acute</td>
<td>4-5 Gy</td>
<td></td>
<td>G-CSF 400-300 μg BID/QD day 22-?</td>
<td>Recovered</td>
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<td>Istanbul, Turkey, 1998</td>
<td>Co-60; acute</td>
<td>2-4 Gy (1&lt;sup&gt;st&lt;/sup&gt; 5 patients) 1-2 Gy (patients 6&amp;7)</td>
<td>7 out of 10 exposed</td>
<td>G-CSF 8 μg/kg/day (5 patients) 5 μg/kg/d (2 patients) day 30-41 (4 patients) day 30-36 (3 patients)</td>
<td>ANC recovery in 4-11 days; lymphocytes slower</td>
</tr>
<tr>
<td>Yanango, Peru, 1999</td>
<td>Ir-192; protracted</td>
<td>Very high local dose; 80-120 Gy to femur</td>
<td>1</td>
<td>GM-CSF day 34-42</td>
<td>Lymphocytes low till D+45</td>
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<td>Tokai-mura, Japan</td>
<td>Criticality</td>
<td>A, B, C:</td>
<td>3</td>
<td>A: G-CSF 100 μg 1\textsuperscript{st} day; none day 2-6; restarted day 7</td>
<td>A: mild dyspnea and rash 1\textsuperscript{st} day; B: rash; C: no Sx stated; A&amp;B: mild response to G-CSF; C: good response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.5 γ, 5.4 n</td>
<td></td>
<td>B: 100, then 500 μg till?; C: day 2-28 (tapered)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 γ, 2.9 n</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1.3 γ, 0.8 n</td>
<td></td>
<td></td>
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- γ = Grays
- n = Nanocuries

1 \textsuperscript{st} day: First day; none day 2-6: None day 2-6; restarted day 7: Restarted day 7; then 500 μg till?: Then 500 μg till?; day 2-28 (tapered): Day 2-28 (tapered)
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<td>Henan Province, China 1999</td>
<td>Co-60; protracted (24 hours)</td>
<td>6.1; 3.4; 2.4 Gy</td>
<td>3 (out of 7 exposed)</td>
<td>GM-CSF 400 μg/m² days 9-37; 200 μg/m² days 18-36; 400 μg/m² days 26-35</td>
<td>All recover after 83 days</td>
</tr>
<tr>
<td>Mit Halfa, Egypt, 2000</td>
<td>Ir-192; protracted (7+ weeks)</td>
<td>5-6, 7.5-8 Gy (died) 3.5-4 Gy (survived)</td>
<td>5 survivors</td>
<td>G-CSF 10 μg/kg/d “Late and prolonged”</td>
<td>Thought to have enhanced survival</td>
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<td>Nueva Aldea, Chile, 2005</td>
<td>Ir-192; acute</td>
<td>1-2 G.2-4.8y</td>
<td>1</td>
<td>G-CSF days 4-6</td>
<td>All WBCs increased 2-4 days of Rx</td>
</tr>
<tr>
<td>Belgium, 2006</td>
<td>Co-60; acute</td>
<td>4.2-4.8 Gy</td>
<td>1</td>
<td>Peg-G-CSF day 28</td>
<td>Dramatic increase in leukocytes</td>
</tr>
<tr>
<td>Senegal, 2006</td>
<td>Ir-192; protracted</td>
<td>3.4 Gy</td>
<td>1 (63 exposed)</td>
<td>Peg-G-CSF 2 months</td>
<td>Recovered</td>
</tr>
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Mixed Field Irradiation

- Mixed field irradiation (MFI) affects medical effectiveness of countermeasures:
  - Pegylated G-CSF: effective at 4 hours for both; somewhat effective at 24 hr for gamma but not MFI
  - ALXN successfully maintains and recovers platelet counts after gamma irradiation but not MFI
  - Phenylbutyrate, YelO2: enhance neutrophil counts but not survival for gamma, MFI
Consensus Guidelines (U.S.)

- Healthy person, no other injuries: 3-10 Gy
  - Consider 2 Gy as threshold in elderly, children
- Multiple injuries or burns: 2-6 Gy
- Mass casualty scenario: 3-7 and 2-6 Gy resp.
- Continue 14-21 days or until normalization (ANC > 1000/mm-3)
- Dosage:
  - G-CSF: 5 mcg/kg/day
  - Pegylated G-CSF: 6 mg SC single dose
  - GM-CSF: 250 mcg/m²/day
Consensus Guidelines (European)

- Emergency HSC transplant not indicated
- Administer cytokines as early as possible
- Continue 14-21 days
- If aplasia persists, consider HSC
- No consensus reached on TPO, TPO agonists, EPO, SCF, but the consensus may be expanded to include the latter two
Consensus Guidelines (Global)

• Cytokines strongly recommended if:
  • Absorbed dose >2 Gy neutropenia and/or decrease in absolute lymphocyte count <0.5x10E9 cells/liter anticipated for 7 days or longer
  • Initiate within 24 hours of exposure
  • Pegylated G-CSF an alternative to G-CSF/GM-CSF
  • Goal: absolute neutrophil count >1.0x10E9/liter and no signs of infection
  • Only organ system liable to critical failure is the hematopoietic system
Summary

- Colony stimulating factors an important part of treatment of ARS after a mass casualty incident
- Administer as soon as possible, but later if necessary
  - Unlike KI, late or delayed administration does provide benefit
  - Administer till granulocyte counts above 1x10E9/L
  - Expect transient decline if administration interrupted
- Criteria for using G-CSF vs. GM-CSF vs. pegylated compounds not well-defined
- Use of G-CSF/GM-CSF with other hematopoietic recovery compounds has been done, but criteria not set yet
- CSF administration does help short-term recovery and (probably) long-term survival, but there are risks
References


• Gourmelon et al., European Consensus on the Medical Management of ARS…*Health Physics* 98(6):825-832; 2010.