Myeloid Cytokines for Treatment of Acute Exposure to Myelosuppressive Doses of Radiation: Hematopoietic Subsyndrome of Acute Radiation Syndrome (H-ARS)

Key Clinical Information

- The goals of using a myeloid colony-stimulating factor for radiation-induced myelosuppression are to:
  - Improve survival of adults and children exposed to myelosuppressive doses of radiation
  - Shorten the duration of severe neutropenia
  - Minimize the severity of neutropenia-associated complications, including infection

- Initiation of treatment in a radiation incident should be strongly considered for patients who:
  - Are likely to have received ≥2 gray (Gy) whole body exposure or ≥2 Gy significant partial body exposure
  - Are likely to have an absolute neutrophil count of ≤500 cells/mm³
  - Will likely have prolonged periods of significant neutropenia (See radiation effects on blood counts diagram).
  - Have significant radiation exposure plus trauma and/or burns, which worsens the clinical outcome compared to radiation exposure alone.

- The CDC is responsible for creating and issuing Emergency Use Instructions (EUIs) regarding drug use in emergencies.
  - The EUI authority allows CDC to facilitate the availability of streamlined information about the use of eligible, approved MCMs needed during public health emergencies without FDA needing to issue an Emergency Use Authorization (EUA).

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<tr>
<th>Cytokine</th>
<th>Key Information</th>
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<tr>
<td><strong>G-CSF: filgrastim</strong> (Neupogen drug label)</td>
<td>• Estimate a patient’s absorbed radiation dose (i.e., level of radiation exposure) based on radiation dose reconstruction information, biodosimetry, if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.</td>
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<tr>
<td></td>
<td>• Administer Neupogen as soon as possible after suspected or confirmed exposure to radiation doses ≥2 Gy. Do NOT delay</td>
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administration of Neupogen if a complete blood count (CBC) is not readily available.

- **Standard dosing when supplies are adequate**
  - Administer 10 mcg/kg/day as a single daily subcutaneous injection in adults and children for the [FDA-approved indication](https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/125031s087lbl.pdf) of acute exposure to myelosuppressive doses of radiation.
  - Continue daily administration until absolute neutrophil count remains greater than 1,000/mm³ (± 1.0 x 10⁹ cells/L) for 3 consecutive (daily) CBCs or exceeds 10,000/mm³ (± 10 x 10⁹ cells/L) after a radiation-induced nadir.
  - Vial sizes are 300 mcg and 480 mcg. For a 70 kg person, 2 vials of either size would be the appropriate dose. It would be reasonable to indicate a maximum dose like 960 mcg OR two vials per dose though this is not uniformly agreed upon. Note that if the appropriate dose requires administration of 2 vials, separate injection sites would be required.
  - See [FDA-approved drug label](https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/125031s087lbl.pdf) for full prescribing information.

- **Strategies for dosing when drug supplies are insufficient to treat all patients at full dose, with plan to return to standard dosing as soon as adequate drug supplies arrive**
  - The standard starting dose for children is 5 mcg/kg which is then titrated for effect as needed.
  - For adults, start with the lower dose of 5mcg/kg/day instead of 10 mcg/kg/day; dose less frequently than daily until adequate supplies arrive to treat all patients at the higher daily dose; stopping drug when ANC reaches 5,000/mm³ (± 5.0 x 10⁹ cells/L) rather than 10,000/mm³ (± 10.0 x 10⁹ cells/L). These recommendations, however, are NOT included in the FDA drug label.

- **Lab monitoring - If possible, obtain a baseline complete blood count (CBC)** prior to administration of first dose and then serial CBCs about every third day until the absolute neutrophil count (ANC) remains greater than 1,000/mm³ (± 1 x 10⁹ cells/L) for 3 consecutive CBCs. Do NOT delay administration of Neupogen if a CBC is not readily available.

<table>
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<th>Pegylated G-CSF: pegfilgrastim (Neulasta drug label)</th>
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<td><strong>Estimate a patient's absorbed radiation dose</strong> (i.e., level of radiation exposure) based on radiation dose reconstruction information, biodosimetry, if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.</td>
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- **Administer Neulasta** as soon as possible after suspected or confirmed exposure to radiation doses ≥2 Gy. Do NOT delay administration of Neulasta if a CBC is not readily available.

- **Standard dosing - when supplies are adequate**
  - In *adults and children weighing ≥45 kg*, two doses, 6 mg each, administered subcutaneously one week apart for the **FDA-approved indication** of acute exposure to myelosuppressive doses of radiation.
  - In *pediatric patients weighing less than 45 kg*, refer to **table in Neulasta drug label** for dose calculated by weight. Administer two doses of drug subcutaneously one week apart.
  - See drug label for specific recommendations about how the prefilled syringe with 0.6 mL (6 mg) should be used, especially since doses of less than 6 mg are recommended for children weighing less than 45 kg.
  - See **FDA-approved drug label for full prescribing information**.

- **Strategies for dosing when drug supplies are insufficient to treat all patients at full dose, with plan to return to standard dosing as soon as adequate drug supplies arrive**
  - Senior medical incident managers might recommend giving the first dose of Neulasta (day 1) and require a CBC prior to the second dose (day 8) in order to consider whether the second dose is necessary or possibly delay it. Subject matter experts recommend NOT administering the second dose if the ANC exceeds 5,000/mm³ (= 5.0 x 10⁹ cells/L). These recommendations, however, are NOT included in the FDA drug label.

- **Lab monitoring** - If possible, obtain a baseline CBC with differential prior to administration of the **first** dose. A CBC should be obtained prior to administration of the **second** dose of Neulasta. Subject matter experts recommend NOT administering the second dose if absolute neutrophil count is greater than 5,000/mm³ (= 5.0 x 10⁹ cells/L), regardless of drug scarcity. Do NOT delay initial administration of Neulasta if a CBC is not readily available.

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**GM-CSF: sargramostim (Leukine drug label)**

- **Estimate a patient's absorbed radiation dose** (i.e., level of radiation exposure) based on **radiation dose reconstruction information**, **biodosimetry**, if available, or **clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics**.

- **Administer Leukine** as soon as possible after suspected or confirmed exposure to radiation doses ≥2 Gy.
• **Standard dosing** – Leukine is a subcutaneous injection administered once daily as follows:
  o 7 mcg/kg in adult and pediatric patients weighing greater than 40 kg
  o 10 mcg/kg in pediatric patients weighing 15 kg to 40 kg
  o 12 mcg/kg in pediatric patients weighing less than 15 kg
  o Continue administration of Leukine until absolute neutrophil count remains greater than 1,000/mm$^3$ ($= 1.0 \times 10^9$ cells/L) for 3 consecutive CBCs or exceeds 10,000/mm$^3$ ($= 10 \times 10^9$ cells/L) after a radiation-induced nadir.
  o See FDA-approved drug label for full prescribing information.

• **Lab monitoring** - Obtain a baseline CBC with differential and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm$^3$ for three consecutive CBCs. Do NOT delay initial administration of Leukine if a CBC is not readily available.

G-CSF = granulocyte colony-stimulating factor
GM-CSF = granulocyte-macrophage colony-stimulating factor