National Institute of Allergy and Infectious Diseases

Beebe Symposium: 30 Years After the Chernobyl Accident

Advances in Research: In Countermeasures

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National Institute of Allergy and Infectious Diseases

Radiation-Nuclear Countermeasures Programs

- Goal: Advance development of medical countermeasures (MCMs) that can be used following a radiological/nuclear incident
- Drug/biologics approval via US FDA Animal Rule, which allows for approval when human clinical studies are unethical or unfeasible
- Government agencies (HHS: BARDA, NIAID; DoD) provide funding for research and development



Product Development Pathway



NIAID program capabilities are in blue.

Natural History of Radiation Injury: Mortality



Anno, et al. *Health Phys* 84(5): 565-575; 2003

Farese, et al., *Radiat Res* 179(1):89-100, 2012.



Natural History of Radiation Injury: Neutrophil Response



Time (Days) After Irradiation

Baranov, et al., Stem Cells 13(suppl 1):69-77, 1995.



Farese, et al., *Radiat Res* 179(1):89-100, 2012.

Treatments: Radiation Accidents

- Five reported accidents (18 patients analyzed) showed bone marrow failure, documentation of cytokine use and demonstration of effect
- Leukocyte Growth Factors (e.g., G-CSF, GM-CSF) used in approximately 13 radiation incidents
- Limitations: few subjects, inconsistent cytokine use (type used, timing); lack of control patients
- Data suggestive of effect, but not conclusive; consistent with controlled animal trials

FDA Advisory Committee Briefing Document, 2013. Dainiak, et al., *Disaster Med Public Health Preparedness*, 5(3):202-212, 2011.



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Neupogen (Filgrastim, @ 10 µg/kg/day) Treatment Increases Survival in Irradiated Rhesus Macaques



FDA Advisory Committee Meeting May 3, 2013

 Question: Considering the known filgrastim effects in the chemotherapy setting, the NIAID study data, and assuming filgrastim would be administered in a clinical dose regimen similar to that evaluated in the NIAID study, is filgrastim therapy reasonably likely to produce clinical benefits in humans exposed to radiation that is likely to induce myelosuppression during or following a radiological/nuclear incident?

Vote: 17-1 in favor



Neupogen® Package Insert Change, March 2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEUPOGEN safely and effectively. See full prescribing information for NEUPOGEN.

NEUPOGEN[®] (filgrastim) injection, for subcutaneous or intravenous use Initial U.S. Approval: 1991

RECENT MAJOR CHANGES		
Indications and Usage (1.6)	03/2015	
Dosage and Administration (2.5)	03/2015	

------INDICATIONS AND USAGE-----NEUPOGEN is a leukocyte growth factor indicated to

 Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) (1.6)



Neulasta (Pegfilgrastim, @ 300 µg/kg, d1 & d8) Treatment Increases Survival in Irradiated Rhesus Macaques



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Neulasta® Package Insert Change, November 2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEULASTA safely and effectively. See <u>full prescribing information</u> for NEULASTA.

NEULASTA[®] (pegfilgrastim) injection, for subcutaneous use Initial U.S. Approval: 2002

RECENT MAJOR CHANGES		
•	Indications and Usage (1.2)	11/2015
•	Dosage and Administration (2.1, 2.2, 2.3)	11/2015
•	Warnings and Precautions (5.6, 5.7, 5.8)	09/2015
•	Dosage and Administration (2.4, 2.5)	12/2014
•	Warnings and Precautions (5.4)	12/2014

-----INDICATIONS AND USAGE-----

Neulasta is a leukocyte growth factor indicated to

 Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). (1.2)



Advances Since Chernobyl

- Additional data in patients, animal models
- US FDA drug/biologic approval process
- US Strategic National Stockpile
- Development of scenarios
- Concept of operations
- Two MCMs approved for acute radiation syndrome



Future Directions/Challenges

- Developing additional MCMs
- Identification of affected individuals (dosimetry)
- Managing mass casualties
- Special populations

