A Joint Meeting of the FDA Medical Imaging Drugs Advisory Committee and the Oncologic Drugs Advisory Committee

May 3, 2013

Leukocyte Growth Factors (LGFs) as Treatments for Radiation-induced Myelosuppression associated with a Radiological/Nuclear Incident

FDA Introductory Remarks

Dwaine Rieves, MD
Director, Division of Medical Imaging Products

Definitions & Background

Leukocyte growth factors (LGFs):

- stimulate proliferation and differentiation of normal white blood cells (leukocytes)

FDA-licensed LGFs:

- filgrastim (Neupogen)
- sargramostim (Leukine)
- pegfilgrastim (Neulasta)
- tbo-filgrastim

Definitions & Background

LGF indications in certain chemotherapy-induced neutropenia (CIN) settings:

- decrease duration of severe neutropenia/incidence of serious infection/febrile neutropenia

No current LGF indications in radiation-injury settings

Radiological/Nuclear incident:

- "release of radioactive material from a deliberate act, an accident, or general mismanagement…"*

*2008 Nuclear/Radiological Incident Annex Report

Why This Meeting?

NIAID submission of data from a non-human primate study that reports filgrastim, in comparison to a vehicle control, improved 60-day survival among lethally irradiated animals.

These data are:

- **The only detailed "new" data for vetting**
- **Considered in the context of previously established LGF nonclinical and clinical effects**
- **Considered under "Animal Rule" expectations**

The "Animal Rule"

- **2002 Final Rule: "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible"**

- **Focus on efficacy extrapolation from nonclinical studies**

- **Safety based on nonclinical *as well as* clinical data**

Criteria for Approval/Licensure Under the Animal Rule

- **The nonclinical study results must establish that the drug is reasonably likely to produce clinical benefit in humans.**
- **Studies are adequate and well-controlled.**
- **Reasonably well-understood pathophysiological mechanism of the toxicity of the substance [*radiation*] and its prevention or substantial reduction by the product.**

Further…

Criteria for Approval/Licensure Under the Animal Rule

- **The effect is demonstrated in more than one animal species expected to react with a response predictive of humans unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.**
- **The animal study endpoint is clearly related to the desired benefit in humans, generally enhancement of survival or prevention of major morbidity.**

And…

Criteria for Approval/Licensure Under the Animal Rule

- **The data or information on kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.**

Prior FDA Product Approvals Based on Efficacy in Animal Models

Setting	*Product/year approved*
Anthrax	Ciprofloxacin (2000) Levofloxacin (2004) Raxibacumab (2012)
Plague	Levofloxacin (2012)
Botulism	Botulism antitoxin heptavalent (2013)
Soman nerve gas	Pyridostigmine bromide (2003)
Cyanide	Cyanokit (2006)

Today: LGFs in the Radiological/Nuclear Incident Setting

- **Multiple presentations**
- **Key question, a focus on data from NIAID study of filgrastim:**

…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?

- **Other discussion topics:**
  - **Strengths & weaknesses of data/information**
  - **NIAID study efficacy implications for other LGFs**

Agenda

- **Guest speakers:**
  - **Dr. Richard Hatchett**
  - **Dr. Nicholas Dainiak**
- **NIAID**
- **FDA comments**
- **LGF manufacturer comments**

….then, after lunch…

- **Clarifications and FDA questions**

Analytical Review of Study AXG15

Lan Huang, Ph.D.
Mathematical Statistician
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Outline

- Study Design
- Primary Endpoint – Survival
- Secondary Endpoints – Absolute neutrophil count (ANC), Platelets
- Other Parameters – Febrile Neutropenia (FN), Transfusion, Supportive Care, Safety

Study Design

- Randomized, two-arm study, vehicle-controlled, blinded
- Two arms – Neupogen, vehicle

- Primary endpoint: survival at Day 60 after radiation
- Primary analysis: Chi-square test

- Interim analysis (mortality)
  - Lan-Demets version of the O'Brien-Fleming boundary was met (p-value < 0.0229)
  - Study stopped for early evidence of efficacy

- 46 out of planned 62 animals were enrolled and studied

Information on Death

- 3 animals in the control group were found dead during the study period (days<60)
  - survival times are 11 days, 17 days, 18 days
- 15 animals were euthanized (10 control, 5 Neupogen)

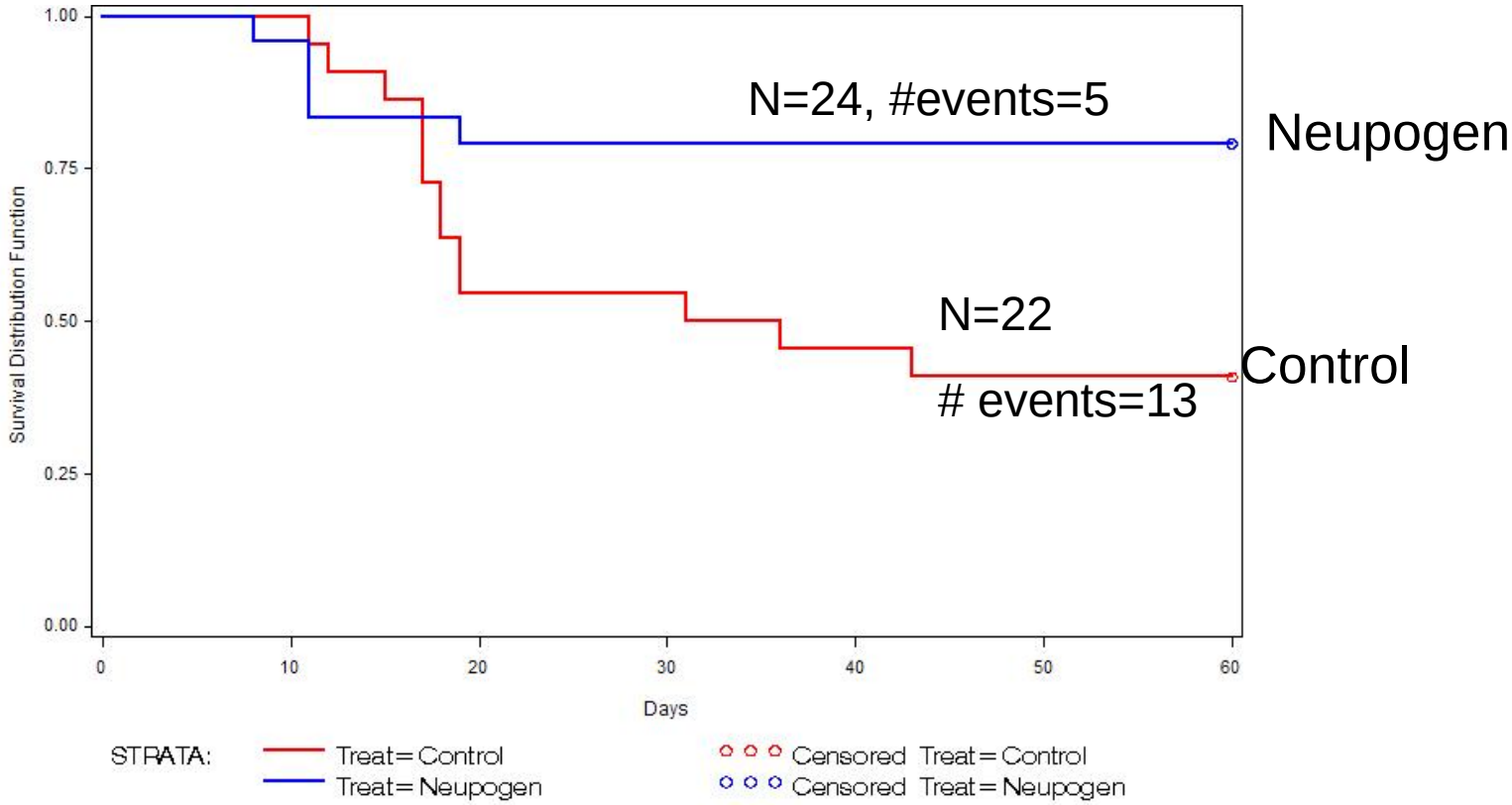
Mortality Comparison

Chi-Square Test: two-sided p-value = 0.0079

Exact Chi-Square Test: two-sided p-value = 0.0147

	Survival	Death	Total
Control	9 (41%)	13 (59%)	22
Neupogen	19 (79%)	5 (21%)	24
Total	28	18	46

Survival Analysis: Kaplan-Meier and Log-Rank Test



Log-rank test: Nominal p-value=0.018.

Baseline Information

	Control	Neupo
Gender		
M	18	20
F	4	4

	Control	Neupo
Source		
TS	12	7
R	10	17

	Control	Neupo
Rad Group		
1	4	6
2	6	1
3	1	5
4	5	4
5	4	4
6	2	4

Exploratory Survival Analyses

- Cox model with treatment only (unadjusted model)
- Analyses with baseline adjustment
  - Multivariate Cox model with treatment + individual baseline variables
  - Propensity score (PS) approaches

Exploratory Survival Analyses

Models	HR (Neup vs. Con)	95% CI
Unadjusted Cox Model	0.31	(0.11, 0.88)
Multivariate Cox Model	0.25	(0.08, 0.77)
PS-adjusted (linear term) Cox Model	0.26	(0.08, 0.80)
PS-adjusted (2 strata) Cox Model	0.31	(0.10, 0.99)
PS-adjusted (Cox model on 28 animals with matching PS scores)	0.27	(0.06. 1.29)

Secondary Endpoints on ANC and PLT

- Neupogen significantly reduced the duration to recovery in terms of ANCs (from ANC<500/µL or <1000/µL to ≥500/µL or 1000/µL for 3 consecutive day)

- Neupogen significantly reduced the duration to recovery in terms of Platelets (from PLT<20,000/µL to PLT≥20k/µL for 3 consecutive days)

Other Parameters

- Neupogen had fewer febrile neutropenia events compared with control (19/24=79% vs. 20/22=91%), but not significantly.
- The frequency of transfusions and the transfusion volume were similar in Neupogen and Control groups.
- No data on the degree of care within each subject – limitation.
- No significant safety findings were identified
  - Measured activity, hemorrhage, histopathology (bone marrow, lung, liver, small intestine, and large intestine).

Conclusion

Neupogen is shown to be efficacious in improving the 60-day survival for non-human primates with total body irradiation (TBI).

Use of Leukocyte Growth Factors for Radiation-Induced Myelosuppression

Summary

Of FDA Reviews

May 3, 2013

William Dickerson, MD
Division of Medical Imaging Products

FDA Reviews

-Reviews of NIAID Study AXG15

-Reviews of Published Literature on use of Leukocyte Growth Factors (LGFs):

- In Animal Studies
- In Radiological/ Nuclear Accidents
- In Radiation Oncology Patients

Reference: FDA Briefing Document for the Joint MIDAC/ODAC Meeting, May 3, 2013

NIAID Study AXG15 FDA Reviewer Conclusions

Clinical, nonclinical, and statistical reviewer analyses **support the NIAID study's primary endpoint finding of improved 60-day survival** among NHPs receiving filgrastim, compared to NHPs receiving vehicle alone.

Reference: FDA Briefing Document for the Joint MIDAC/ODAC Meeting, May 3, 2013; pp 13-117

FDA Reviews of Published Literature on Use of LGFs for Radiation-Induced Myelosuppression

1. In Animal Studies

by Yanli Ouyang, PhD

2. In Radiological/ Nuclear Accidents

3. In Radiation Oncology Patients

Reference: FDA Briefing Document for the Joint MIDAC/ODAC Meeting, May 3, 2013; pp 118-186

G-CSF in Animal Studies, Survival and/or WBC Recovery

- G-CSF enhanced survival in canine and mouse models
- G-CSF enhanced WBC recovery in all animal species
  - Decreased duration of neutropenia and time to ANC recovery (a few days)
  - Increased WBC counts

GM-CSF in Animal Studies, Survival and/or WBC Recovery

- GM-CSF enhanced survival in some but not in all studies.
- GM-CSF enhanced WBC recovery in majority of studies conducted; same endpoints as G-CSF.

Limitations of Animal Studies G-CSF and GM-CSF

- PK studies inadequate for animal-human dose conversion
- Difficulty in verifying data accuracy and integrity
- Study design deficiencies
  - Small sample sizes (n=2-4) in NHP and dog studies; no concurrent controls; insufficient information on supportive care and criteria for euthanasia

Conclusion
Leukocyte Growth Factors in Animal Studies

G-CSF: Despite some limitations, published literature overall **supports the survival and WBC recovery benefit for hem-ARS**.

GM-CSF: Published literature **supports WBC recovery benefit for hem-ARS**. The results are **less consistent regarding the survival benefit**.

FDA Reviews of Published Reports of LGF Use for Radiation-Induced Myelosuppression

1. In Animal Studies
2. **In Radiological/ Nuclear Accidents**

   by William Dickerson, MD
3. In Radiation Oncology Patients

Reference: FDA Briefing Document for the Joint MIDAC/ODAC Meeting, May 3 2013; pp 134-154

LGF Use in Rad/Nuc Accidents

- 13 Rad/Nuc accidents identified 1986-present where LGFs were used
- 48 victims treated with LGFs
  - 17 received GM-CSF (first used 1986)
  - 16 received G-CSF (first used 1996)
  - 9 received both GM-CSF & G-CSF (1999, 2000)
  - 2 received both GM-CSF and IL-3 (1990,1991)
  - 2 received peg-G-CSF with SCF (2006)
  - 1 received G-CSF & Stem Cell Transplant (1999)
  - 1 recd G-CSF, GM-CSF, & Cord Blood (1999)

LGF Use in Rad/Nuc Accidents

- Dose Range for Victims: 0.9 to > 16 Gray
- Timing for start of LGF: immediate versus weeks after radiation exposure
- Deaths: 11 of 48 victims, some died within days and others as late as 197, and 211 days after radiological/ nuclear incident.

Rationale for Use Of LGFs in Rad/Nuc Accidents

- Early Recommendation: Theoretical
- Present Recommendations: Consensus Papers:
  - Strategic Natl Stockpile Working Group, 2004
  - ASCO Guidelines for WBC Growth Factors, 2006
  - European Consensus Conference, 2006
  - World Health Organization (Dainiak, 2011)

Conclusion
LGF Use in Rad/Nuc Accidents

- LGFs have been used in humans after several Rad/Nuc accidents
  - No randomized studies in humans
  - Wide variation rad dose, time to initiation of drug, drug dose, and drug duration
  - Impression that LGFs may have helped, and did not hurt.
- Data too sparse to evaluate efficacy

FDA Reviews of Published Reports of LGF Use for Radiation-Induced Myelosuppression

1. In Animal Studies
2. In Radiological/ Nuclear Accidents
3. **In Radiation Oncology Patients**

by Cynthia Welsh, MD

Reference: FDA Briefing Document for the Joint MIDAC/ODAC Meeting, May 3, 2013; pp 155-186

Literature Review of LGF Use in Radiation Oncology Patients

- Only 4/28 articles on use of RT+LGF had WBC as an endpoint
  - 25 patients RT + G-CSF (no chemo)
  - No randomized trials
  - Prophylactic administration: 2 articles
  - Therapeutic administration: 2 articles
- WBCs in the G-CSF-treated patients increased after administration

Limitations on Review Of Use of LGFs in RT Patients

Multiple confounding variables

- Differing RT doses, fractionation, & volumes
- Differing LGF administration regimens and doses
- Differing diseases treated
- Variable chemotherapy history
- Variable study endpoints: Change in WBC, dysphagia, PEG placement. Not FN

Conclusion of Review On Use of LGFs in RT Patients

- LGFs after radiation exposure increased WBCs at least temporarily. Unknown clinical significance
- We can not extrapolate results from effect on an older population being treated with fractionated, limited volume radiation therapy to a healthier population which may receive a large single dose of TBI in a Radiological/Nuclear Incident.

I THANK YOU

and the FDA's
Division of Medical Imaging Products,
Division of Hematology Products, and
Office of Counterterrorism and Emergency Coordination