Evidence-Based Recommendations for the Use of Cytokines in a Radiological/Nuclear Incident

FDA Advisory Committee Meeting
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Disclosures

- Relevant financial relationships – NONE
- WHO Consultancy: views and recommendations are those of consultants, and not of WHO, IAEA, CDC, Bundeswehr, HPA, NIH, DHS, DOD.
- Cytokines and other therapeutics not approved by regulatory bodies (FDA, EMA, etc).

Objectives

1. Describe process for WHO consultancy and methods for assessment of quality of evidence to manage ARS, including:
   - ✓ Data Sources
   - ✓ Study Selection
   - ✓ Data Extraction
   - ✓ Data Synthesis

2. Present consensus recommendations of this international panel of experts for optimal management of the hematopoietic syndrome (HS) based upon evidence in the published literature.

3. Update outcomes in HS treated with cytokines based on more recent publications.

Hematopoietic Syndrome

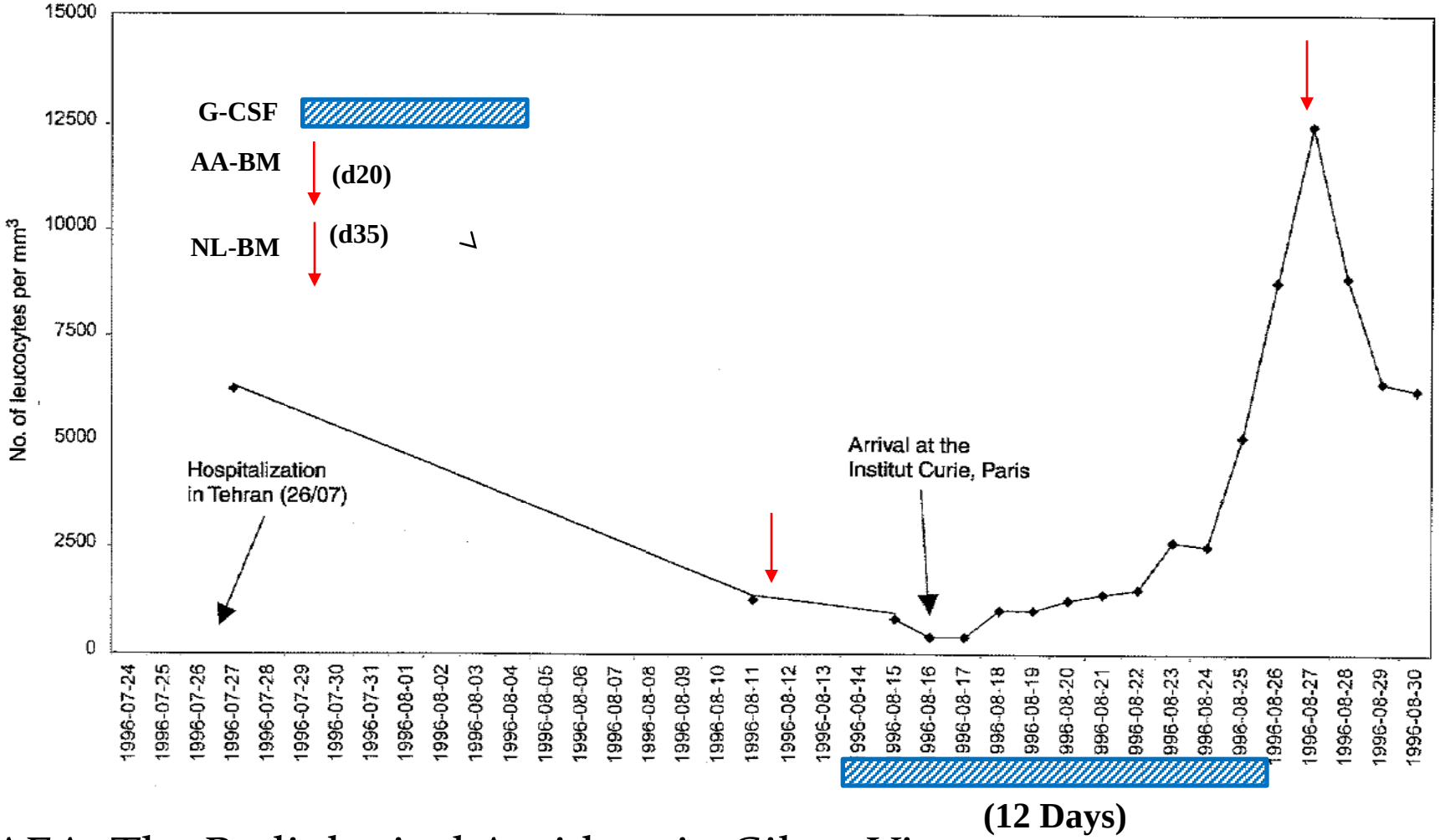
Clinical diagnosis: individuals presenting with ≥ 1 new-onset cytopenias in the setting of whole-body or significant partial-body acute radiation exposure

Levels of Hematopoietic Toxicity

Symptom or Sign	Degree 1	Degree 2	Degree 3	Degree 4
Lymphocyte changes †	$\geq$ 1.5 x 10^9 cells/L	1-1.5 x 10^9 cells/L	0.5-1 x 10^9 cells/L	<0.5 x 10^9 cells/L
Granulocyte changes ‡	$\geq$ 2 x 10^9 cells/L	1-2 x 10^9 cells/L	0.5-1 x 10^9 cells/L	<0.5 x 10^9 cells/L
Thrombocyte changes §	$\geq$ 100 x 10^9 cells/L	50-100 x 10^9 cells/L	20-50 x 10^9 cells/L	<20 x 10^9cells/L
Blood Loss	Petechiae, easy bruising, normal hemoglobin level	Mild blood loss with <10% decrease in hemoglobin level	Gross blood loss with 10%- 20% decrease in hemoglobin level	Spontaneous bleeding or blood loss with > 20% decrease in hemoglobin level

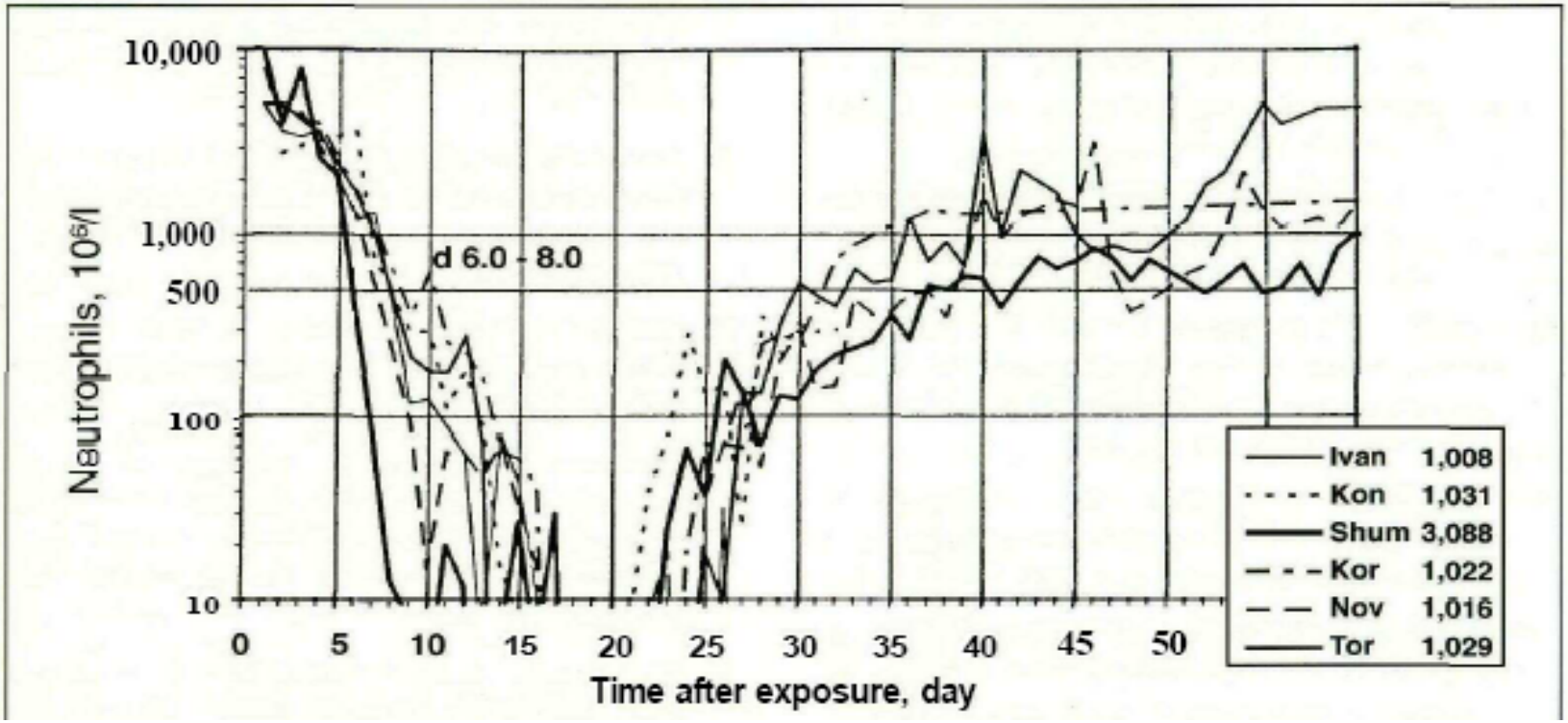
† Reference value, 1.4-3.5 x 10^9 cells/L.
‡ Reference value, 4-9 x 10^9 cells/L.
§ Reference value, 140-400 x 10^9 cells/L.

WBC Counts in Case from Gilan, Iran Incident (1996)



IAEA, The Radiological Accident in Gilan, Vienna, 2002.

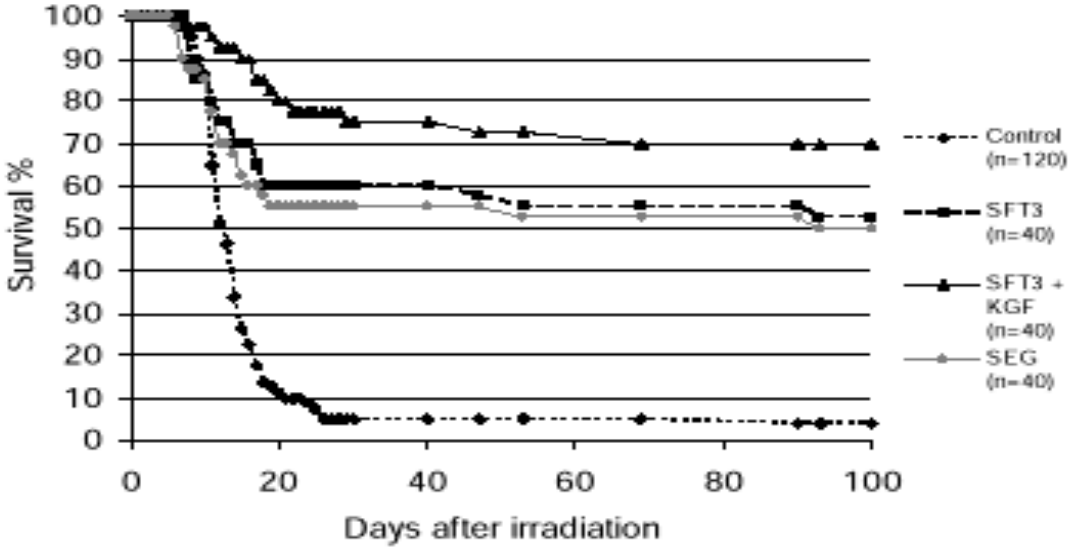
Spontaneous Recovery of PMN Counts in 5 Liquidators Chernobyl, 4/26/1986



Shown are PMN counts for five individuals who had a PMN count of 500 per mm^3 6-8 days after exposure and who lived greater than 30 days. In no case was therapy with cytokines or stem cell transplanation administered.

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

Effects of GF Combinations on Survival of Irradiated Mice (9Gy)



SEG = SCF + EPO + G-CSF.

SFT3 = SCF + Flt ligand + TPO + IL-3.

Herodin F et al., Exp Hematol 35: 28, 2007

Importance of Radiation Dose

Dose	Mortality*	Syndromes
1-2 Gy	Close to 0% at ≤ 1 Gy	Onset of HS and GIS Reversible
3-4 Gy	LD 50/60 Without Rx	Onset of CNS Symptoms
6-7 Gy	LD 50/60 With Rx	Progression of Severity of Sub-syndromes
> 10 Gy	100%	Irreversible

* Mortality from radiation

Guidelines for Cytokine Treatment in Radiological Victims

Small Volume Scenario (≤100 Casualties)

Healthy Individual, no other injuries	3 - 10[a]
Multiple Injuries and/or burns	2 - 6[a]

Mass Casualty Scenario ≥100 casualties)

Healthy Individual, no other injuries	3 - 7[a]
Multiple Injuries	2 - 6[b]

Notes: a) Consider initiating therapy at lower exposure dose in non-adolescent children and the elderly. Initiate G-CSF or GM-CSF treatment in those victims who develop an absolute neutrophil count <500 cells/mm^3 and who are not already receiving a CSF. **b)** If resources available.

Waselenko et al., Ann Intern Med 140:1037 (2004)

U.S. SNS Radiation Working Group

Recommended Doses of Cytokines

Cytokine	Adults	Pediatrics	Pregnancy*	Precautions
G-CSF or Filgrastim	5 ug/kg per day SC, and continued until ANC >1,000 cells/mm^3	5 ug/kg per day SC, and continued until ANC >1,000 cells/mm^3	Class C+ (same as adults)	Sickle cell hemoglobinopathies, significant coronary artery disease, ARDS. Consider discontinuation if pulmonary infiltrates develop at neutrophil recovery.
Pegylated G-CSF or Pegfilgrastim	6 mg, SC x 1 dose	For adolescent >45 kg: 6 mg, SC x 1 dose	Class C (same as adults)	Sickle cell hemoglobinopathies, significant coronary artery disease, ARDS.
GM-CSF or Sargramostim	250 ug/m^2 per day, SC, and continued until ANC >1,000 cells/mm^3	250 ug/m^2 per day, SC, and continued until ANC >1,000 cells/mm^3	Class C (same as adults)	Sickle cell hemoglobinopathies, significant coronary artery disease, ARDS. Consider discontinuation if pulmonary infiltrates develop at neutrophil recovery.

+Class C: Refers to US Federal Drug Administration Pregnancy Category C; studies have shown, teratogenic and/or embryocidal effects in animals but there are no controlled studies in women.

*Experts in biodosimetry must be consulted. Any pregnant patient with exposure to radiation should be evaluated by a health physicist and maternal-fetal specialist for an assessment of risk to the fetus.

Abbreviations: Absolute Neutrophil Count (ANC), Subcutaneous (SC), Acute Respiratory Distress Syndrome (ARDS).

US – European Consultation Workshop *

First responders with an ANC < 500 should receive G-CSF. It should begin a.s.a.p. after documentation of ANC and continue for 2-3 weeks.

Victims in whom external dosimetry demonstrates a dose of 3 Gy (or 2 Gy with combined injury) should receive G-CSF.

Pegylated G-CSF should not be used.

* Fliedner TM et al, Stem Cells 2009;27:1205-11

Erythropoietin in ARS

Consensus Group	Recommendations
U.S. Strategic Natl. Stockpile Radiation Working Group	Not routinely indicated. Consider use in patients with persistent anemia (Hct < 30%). Consider iron supplementation when EPO is used.
U.S. – European Consultation Workshop	Not routinely indicated. Consider use in patients with external injury and blood loss (Hgb < 9 gm/dl).

Recommendations for Use of CSFs (American Society of Clinical Oncology)

1. Febrile neutropenia in patients who are at high-risk for infection-associated complications, or whose prognostic factors predict for poor outcome.

2. Some cases of dose-dense chemotherapy (dose intensification).

3. Mobilization of progenitors cells from PB to shorten period of neutropenia after cytoreduction and transplantation.

4. Reduction of duration of neutropenia after induction or consolidation chemotherapy for AML.

5. Increase ANC in myelodysplatic syndrome.

6. Treatment of aggressive lymphoma in patients ≥ 65 y/o.

Smith et al., J Clin Oncol 24: 3187, 2006.

ESMO Guidelines Working Group Recommendations for Cytokine Use

Reasonable if	Parameter
Probability of febrile neutropenia is ≥20%.	Affects ANC recovery, fever, infection rate, i.v. abx use and discharge from hospital.
Dose reduction believed to be detrimental to outcome.	Survival

Note: special situations include: ANC < 1.5 due to RT to > 20% of marrow, HIV, patients ≥65 years on a currative treatment regimen, prophylaxis for subsequent infection in the next treatment cycle, dose reduction below threshold and protracted (>7 days) febrile neutropenia, hypotension, sepsis, pneumonia or fungal infection.

Griel et al., Ann Oncol 19 (Supple 2): 116 (2008)

Background and Justification

- Lack of guidelines for many clinical sequelae and variations in treatment recommendations by individual physicians, physician groups and expert panels.

- Limited experience with high-volume (> 10 individuals) scenarios and no clinical experience with mass casualties (>100 individuals) aside from ABS.

WHO Consultancy

- **Panel of experts:** Co-organizers selected subject matter experts from Europe, North America, South America and Asia. Met on March 16-18, 2009.

- **Virtual scenario:** 100-200 individuals require hospitalization. Omitted (1) consideration of pre-hospital treatment and triage, and (2) management of external and internal contamination.

- **Pre-Meeting References:** WHO solicited English language references from each expert. References distributed to all experts before and during (updated references) meetings.

- **Presentations:** Brief (10-15 min) presentations.

- **Discussion and Ranking:** Recommendations discussed in five sessions (1-3 ½ hrs each), followed by ranking of recommendations and assignment of strength of recommendation (via email). Average scores determined for final ranking.

Participants

Austria	-	Elena Buglova
Brazil	-	Nelson Valverde
Canada	-	Holger J. Schünemann
China	-	Ying Liu
		Wei Zhang
France	-	Thierry de Revel
		Patrick Gourmelon
Germany	-	Axel Boettger
		Arthur Ganser
		Viktor Meineke*
		Rita Schneider
Japan	-	Makoto Akashi
		Kazuhiko Maekawa
Luxembourg	-	Helmut Walerius
Russian Federation	-	Mikhail Konchalovski
Sweden	-	Leif Stenke
United Kingdom	-	Nick Gent
		Ray Powles
		Hilary Walker
USA	-	Joseph Albanese
		Judith Bader
		Nelson Chao
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		Martin Hauer-Jensen
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		L. Andrew Huff
		Patricia Lillis-Hearne
		Maria Julia Marinissen
		Fred A. Mettler, Jr.
		Jeffrey Nemhauser
		Alla Shapiro
		David Weinstock
		Douglas White
WHO	-	Zhanat Carr*
		Carlos Dora+
		Maria Neira+
		Annette Nock+
		Luc Noel+
		Maria Perez
		Annette Pruss-Ustum

*

+

Literature Selection and Analysis

1. English – language articles identified in **MEDLINE** and **PubMed**:
   - ✓ Case series and case reports of ARS
   - ✓ RCTs of relevant interventions in non-irradiated individuals.
   - ✓ Controlled studies in irradiated animals.
   - ✓ Recommendations of prior consensus groups.

2. Data extraction:
   - ✓ Grading of Recommendations Assessment Development and Evaluation (GRADE) system used for assessment of evidence supporting use of cytokines and/or HSC transplantation in management of HS.
   - ✓ Narrative review of evidence supporting use of 14 treatment strategies in management of ARS affecting non-hematopoietic organ systems and 3 treatment strategies for management of HS.

Assignment for Quality of Evidence

Assignment	Level	Definition
A	High	Available evidence usually includes consistent results in irradiated or non-irradiated patient or animal populations.
B	Moderate	Available evidence is of moderate quality. It is consistent with beneficial effect on outcomes but studies in humans and/or animals are suboptimal due to inadequate power, inconsistent findings or limited generalizability.
C	Low	Available evidence is of low quality. It is insufficient to assess effects on outcomes due to studies in humans and/or animals having inadequate power, inconsistent findings or limited generalizability.
D	Very low	Available evidence is of very low quality due to lack of studies or to studies in humans and/or animals having inadequate power and/or serious flaws in design, measurement techniques or reproducibility.

Numerical Representation for Strength of Recommendation Based on Net Benefit*

Assignment	Definition	Implication	Practice
1a	Consultancy strongly recommends this practice with a high certainty of substantial net benefit.	Most patients would accept treatment and most clinicians would recommend treatment.	Provide service
1b	Consultancy weakly recommends this practice with a moderate certainty of moderate net benefit.	While most patients would elect treatment, many would refuse it. Many clinicians would not recommend treatment but most would recommend treatment.	Probably provide service
2a	Consultancy strong recommends against this practice since there is a moderate or high certainty of no net benefit	Most patients would refuse treatment, and most clinicians would not recommend treatment.	Do not provide service
2b	Consultancy weakly recommends against this practice routinely. However, the practice should be considered in individual patients with a high or moderate certainty of small net benefit.	While most patients would refuse treatment, many would accept it. Many clinicians would recommend treatment but most would not.	Provide service only if other considerations support it in an individual patient

GRADE

- **Process** reviewed with entire consultancy by Holger J. Schünemann, (Guyatt et al., BMJ 2008; 336:1049).

- **PICO** format for focused questions: Patient problem, Interventions, Comparison and Outcome (Schardt et al., BMC Medical Informatics and Decision Making 2007; 7:16).

- **GRADE Grid** constructed and quality assessed for each management strategy by a single individual (NG) and reviewed by four co-authors (ND, VM, ZC, RS).

- Final recommendations **upgraded or downgraded** based on results of interventions in non-irradiated individuals, controlled animal studies and prior recommendations of subject matter experts.

Major Findings

1. No RCTs of medical countermeasures have been completed for individuals treated with ARS.

2. Use of GRADE analysis of countermeasures for injury to hematopoietic tissue is restricted by lack of comparator groups in man.

Rationale for Cytokines

- Improved levels of circulating neutrophils, platelets and erythrocytes in well controlled experiments in **animals** receiving G-CSF, GM-CSF, thrombopoietin and/or EPO.

- Diminished time to recovery of **human** circulating neutrophils after consolidation chemotherapy for AML and dose-dense chemotherapy (dose intensification) for solid tumors; improved survival in patients with febrile neutropenia and high-risk for infection-associated complications; increased ANC in MDS; shortened period of neutropenia after cytoreduction and transplantation with progenitors mobilized from PB.

Cytokine Studies

Accident Site	Data Set*	
	Complete	Incomplete
1. Goiania, Brazil	√	
2. Tokai-mura, Japan	√	
3. Henan Province, China	√	
4. Istanbul, Turkey	√	
5. Gilan, Iran	√	
6. Mol, Belguin		√
7. Dakar, Senegal		√
8. Concepcian, Chile		√

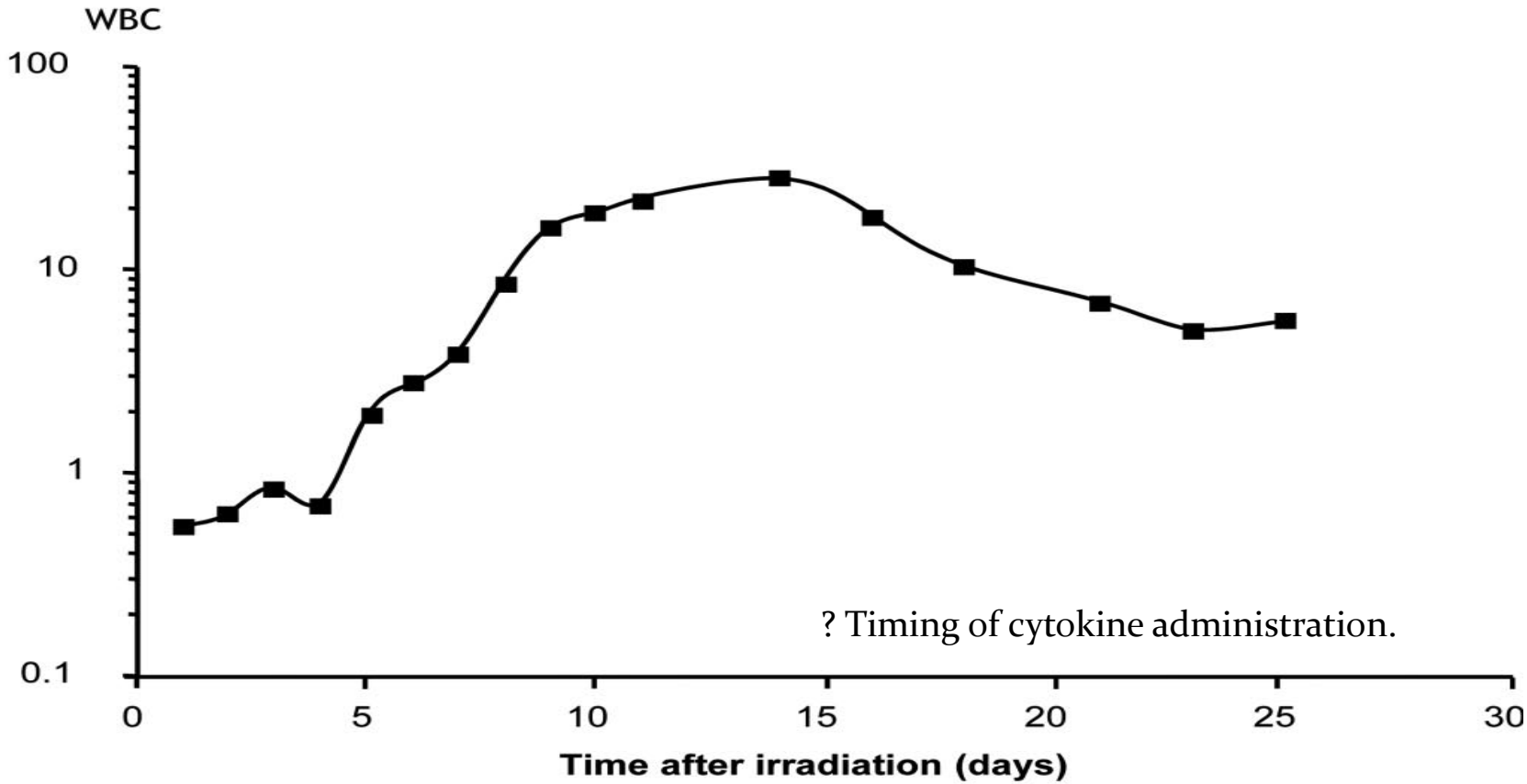
*Data set: (1) establishment of bone marrow failure
(2) documentation of cytokine use
(3) demonstration of effect/no effect on hematopoietic system

Dakar, Senegal

- Unknowingly, a patient was exposed to an insecure ^{92}Ir source over 2 months in **2006**. A highly **heterogeneous** exposure was determined and a whole body dose of **3.1 Gy** was estimated.

- The patient was hospitalized at 1-2 months after exposure with **Grade 3** hematopoietic syndrome (HS). It was believed that the HS was improving based on circulating CD 34+ cells, presence of circulating CFU-GM and BFU-E, and a progressive increase in Flt 3 ligand level. The patient received **peg-G-CSF, peg-EPO and rh-SCF** (Stemgen). "The patient rapidly recovered a normal blood cell count."

WBC Counts in Dakar, Senegal Accident (2006)



Mean dose: 3.4 Gy
Gourmelon P et al, Health Phys 98:825, 2010.

Concepcion, Chile

- While a radiographer dismantled radiography equipment, the source fell from construction platform of a cellulose plant in Nueva Aldea, Concepcion on **12/14/2005**. Scaffolding worker picked up source the next day, showed it to supervisor and electronic alarm dosimeter was activated in the adjacent office.

- Worker A was administered **G-CSF** based on early estimate of whole body dose (**1.3-1.5Gy**). Later estimates based on clinical S+S, cytogenetics and dose reconstruction indicated a lower dose (**0.8-1.0Gy**). G-CSF discontinued after **2 days** of treatment.

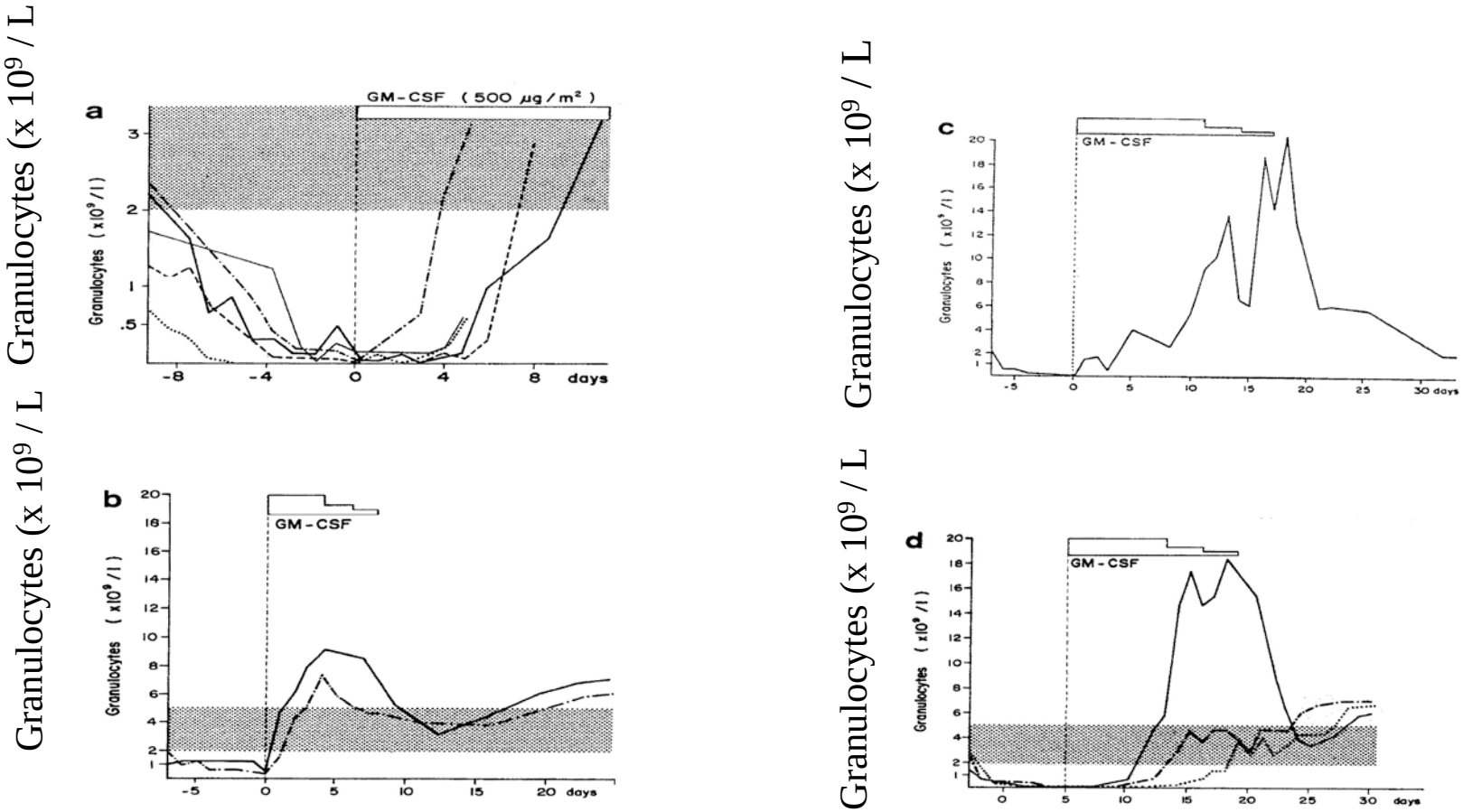
Studies with Cytokines

Study	Estimated WB Dose	Number (Total)	Cytokine (No pts*, Dose)	Importance
1. Goiania, Brazil (1987)	2.5-7.1 Gy (137 Cs source)	10 pts	GM-CSF (8 pts: 2.7-6.0 Gy)	Critical
2. Tokai-mura, Japan (1999)	0.8-5.5 Gy neutrons 1.3 – 8.5 Gy gamma	3 pts (1 pt-PBSCT, 1 pt-CBT +GCSF)	G-CSF (1 pt: 0.8 Gy neutrons 1.3 Gy gamma)	Important
3. Henan Province, China (1999)	2.4-6.1 Gy (60 Co source)	3 pts	GM-CSF (3 pts: 2.4, 3.4, 6.1 + Gy)	Critical
4. Istanbul, Turkey (1998)	0.6-3.1 Gy (60 Co source)	10 pts (5 pts BM failure)	G-CSF (5 pts; 2.2-3.1 Gy)	Critical
5. Gilan, Islamic Republic of Iran (1996)	2.5-3.5Gy (uncertain) (192 Ir source)	1 pt	G-CSF (1 pt:: ? BM recovery already underway)	Not important

*Number of evaluable patients.

+Pt received GM-CSF + EPO.

Responses to GM-CSF Therapy in Victims of Goiania, Brazil Accident, 9/13/87



Recombinant human GM-CSF (500 µg/m^2/day) was administered at a median interval of 32 days (range of 24-38 days) following radiation exposure. Four of eight individuals who received GM-CSF survived. In nearly all cases, growth factor administration resulted in prompt increase in granulocyte count.

Butturini A, et al., Lancet 2: 471-5, 1988

Goiania, Brazil Accident, 9/13/87

- 5/8 patients had good hematological response to cytokines: Doses: **4.0, 2.5, 4.3, 4.4 and 3.0 Gy.**

- 3/8 patients had poor or no hematologic response to cytokines: Doses: **6.0, 6.0 and 5.3 Gy.**

- Death occurred in all cases where GN septicemia developed before onset of cytokine therapy, independent of hematological response.

Tokai-mura Japan Incident (9/30/99)

Patient (Outcome)	Dose (Gy) Neutrons	Y-rays	G-CSF Day	Transplant (Day)
A (Expired d 82)	5.4	8.5	1	PB (d2)
B (Expired- d 210)	2.9	4.5	1	CB (d 9)
C (Survived)	0.8	1.3	2	NA

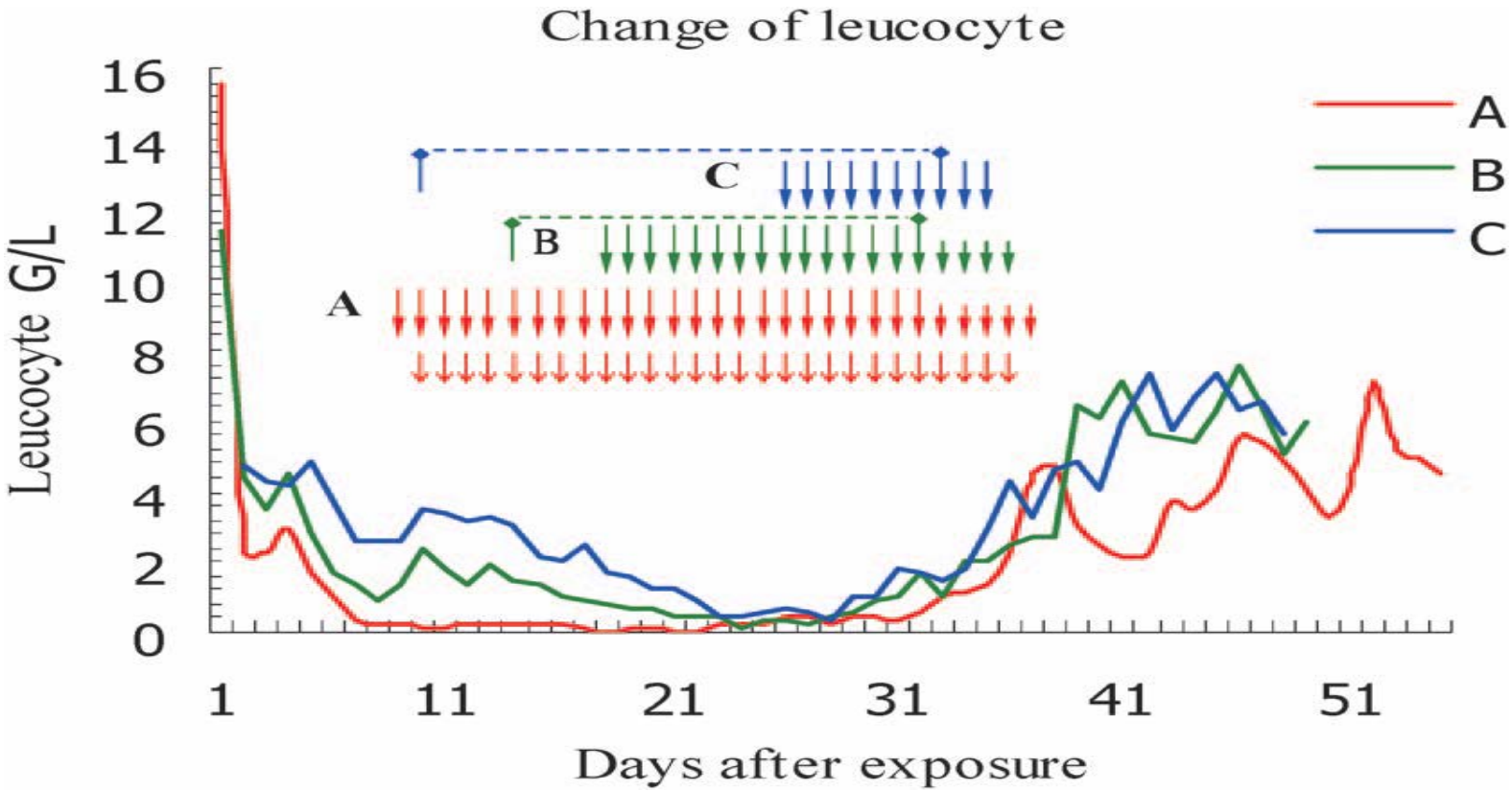
Henan Province, China (1999)

- ^{60}Co radiotherapy equipment was sold as scrap metal. Workers disassembled equipment, found the source. A dealer bought the source, brought it home and placed it near the bed of his wife and son. The 3 individuals developed emesis and 4 days later were admitted to the Hospital of Occupational Disease Prevention. All 3 were treated with cytokines (**GM-CSF -** 2 pts; **G-CSF+EPO -** 1pt), beginning 7, 13 and 22 days after exposure.

- The dose was estimated at **2.4, 3.4 and 6.1 Gy** (and by cytogenetics at **2.6, 2.5 and 5.1 Gy**).

- Excellent documentation of recovery of WBC counts.

WBC Counts in 3 Cases from Henan Province Incident (1999)



↓ GM-CSF for case A, the shorter ↓ indicates the decrement.
↓ GM-CSF for case B, the shorter ↓ indicates the decrement.
↓ GM-CSF for case C, ↓: EPO for case A

Liu Q et al., J Radiat Res 2008;49:6369

Istanbul, Turkey (1998)

- **5 patients with bone marrow failure** were treated with cytokines. Their doses were **2.2, 2.3, 3.1, 2.5 and 2.5 Gy**. GM-CSF therapy was initiated 4 weeks after initial exposure with a good hematological response and clear evidence of a time-related response in each case.

- **5 patients without bone marrow failure** were not treated with cytokines. Their doses were **1.8, 0.9, 0.6, 0.8 and 0.6 Gy.**

Gilan, Iran Incident (1996)

- Iridium source became detached from its drive cable after it was used to image welds on a boiler and pipes of a power plant. The container for the source was mistakenly not locked. The source fell into a trench and was picked up by a worker who placed it into the breast pocked of his coveralls. One hour later, the worker returned the source to the trench. The dose was estimate at **2.5 - 3.5 Gy.**

- When the total WBC count declined to <1,000/mm^3 (day 22), **G-CSF** was initiated. The WBC count increased to 8, 500/mm^3 (day 34) and G-CSF was discontinued.

- "Cytokine therapy is **unlikely to have made a major contribution** to marrow recovery by day 35 because of its relatively late initiation, although it would have assisted in the process. **Marrow recovery was clearly underway already**". [IAEA, The Radiological Accident in Gilan, Vienna, 2002].

Among Individuals with Cytopenia after Exposure to Ionizing Radiation, do Cytokines (G-CSF or GM-CSF) vs. No such Therapy Impact Overall Survival?

Quality assessment			Summary of findings				
			No. of patients				
No. of studies and patients *	Design	Other considerations	No. treated with cytokines / patients	No. not treated with cytokines / patients	Effect[1]	Quality	Importance
5 studies 20 patients identified with bone marrow failure (amongst a total of 27 patients reported with ionising radiation injury by these studies)	observational studies	strong association	18/20 (90%)	2/20 (10%)	Survival observed in 14/18 (78%) treated patients with refractory bone marrow failure Survival observed in 2/2 (100%) patients not treated	⊕⊕⊕○ MODERATE	CRITICAL

*No serious limitations in study, consistency, directness or precision of the 5 studies.

Response Summary (5 Studies)

Dose Range	Survival
≥ 5 Gy	**1/3 patients**
< 5 Gy	**14/15 patients**

Conclusions for Cytokine Use

1. Cytokines are of possible benefit to myelopoiesis when used in patients with absorbed doses of < 5 Gy when the only organ-critical failure is the hematopoietic system.

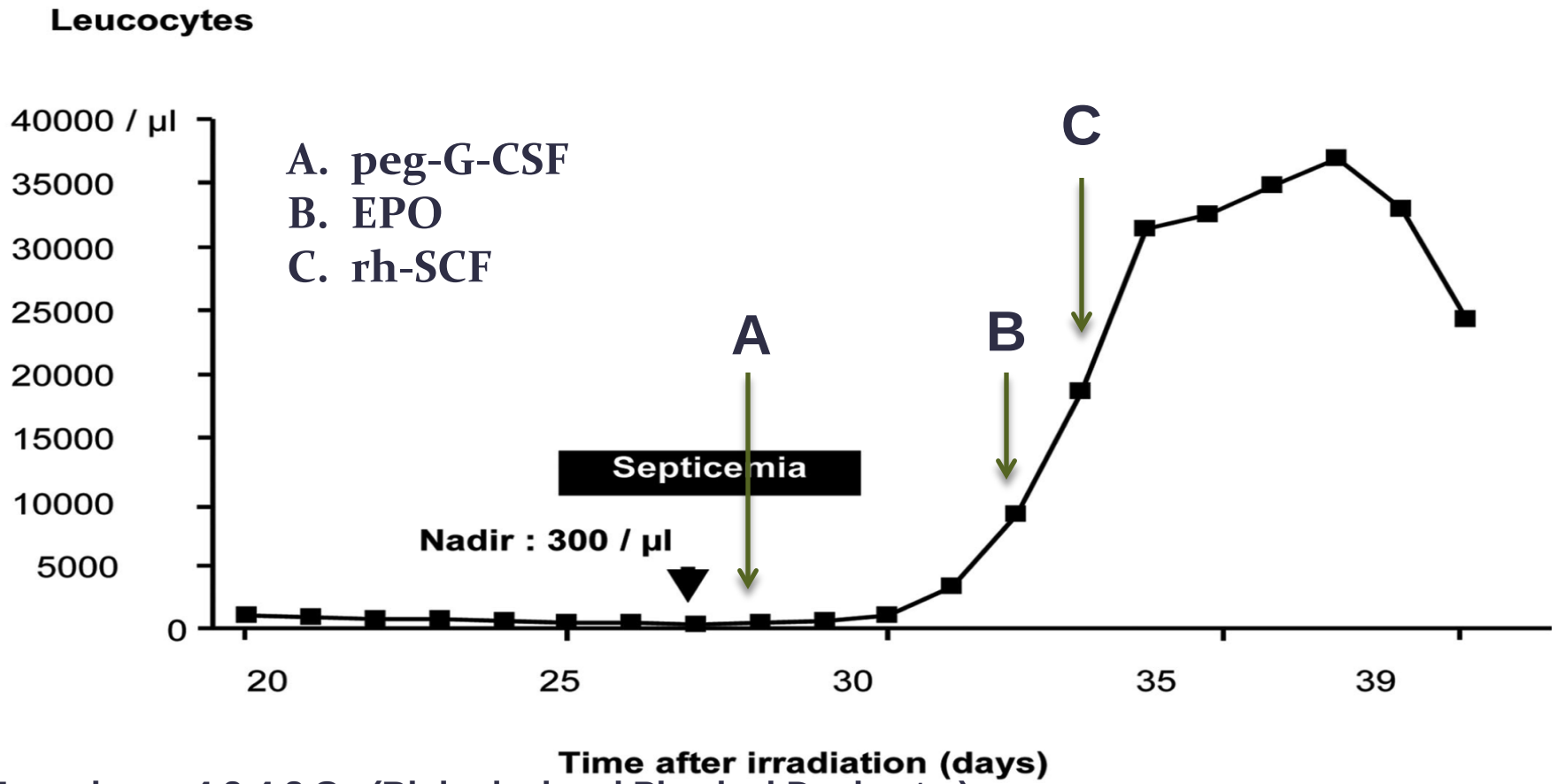
2. The published studies are descriptive without a contemporaneous comparison group. Such studies are not very useful in establishing causality.

Fleurus, Belgium

- Unaware that the ^{60}Co source was partly out of security position, an operator entered the irradiation room of a sterilization facility on **3/11/2006**. The patient was exposed for 22 sec to ^{60}Co [activity: 2.96×10^{16} Bq (800,000 Ci) dose rate of 5,000 Gy/hr]. Exposure was heterogeneous with estimate of whole-body dose of **4.2-4.8Gy**.

- Operator developed **Grade 4** hematopoietic syndrome (HS) at **20 days** post-exposure, and was hospitalized where he received **cytokines** for HS and antibiotics for pseudomonas septicemia.

Cytokine Response in Fleurus, Belgium Accident (2006)



Mean dose: 4.2-4.8 Gy (Biological and Physical Dosimetry)
Gourmelon P et al, Health Phys 98:825, 2010.

Impact of Fleurus, Belgium Case on Response Summary

Dose Range	Survival
≥ 5 Gy	**1/3 patients**
< 5 Gy	**14/15 patients-without case** **15/16 patients-with case**

No change in Conclusions for Cytokine Use

Formulation of Recommendations

The consultants considered the evidence that was extracted from these 5 studies, according to GRADE. They modified their ranks by considering RCTs in un-irradiated humans, results in animal studies, and recommendations of the SNS Working Group and the Combined European – US Consultation Workshop, as permitted by GRADE.

Summary of Recommendations for Treating Hematopoietic Syndrome in Hospitalized Patients with Whole-Body exposure to Ionizing Radiation

Recommendation	Strength of Recommendation
Administer G-CSF or GM-CSF when ANC < 0.500 x 10^9 cells/L	Strong (B-1a)
Administer ESAs when prolonged anemia is present in order to avoid need for red blood cell infusion	Weak (C-1b)

Strength of recommendation was determined by assignment of quality of the evidence (A-High, B-Moderate, C-Low or D-Very Low) and strong (1a) or weak (1b) recommendation in favor of the practice.

Conclusions

1. Robust studies of therapeutic interventions in humans exposed to non-therapeutic radiation are not available and, due to ethical concerns, are unlikely to emerge.

2. Nevertheless, recommendations for specific countermeasures can be made based on assessment of:
   - ✓ Case reports of irradiated individuals.
   - ✓ Case series of irradiated individuals.
   - ✓ RCTs of relevant countermeasures in unirradiated individuals.
   - ✓ Well controlled animal studies.
   - ✓ Recommendations of subject matter experts.

Conclusions (continued)

3. Based on GRADE analysis, a **strong** recommendation was made for the administration of G-CSF or GM- CSF; and a **weak** recommendation was made for the use of ESAs in a radiological/nuclear incident.

First Global Consensus for Evidence-Based Management of the Hematopoietic Syndrome Resulting From Exposure to Ionizing Radiation

Nicholas Dainiak, MD, FACP; Robert Nicolas Gent, MB, ChB, FFPH;
Zhanat Carr, MD, PhD; et al.

Objective: Hematopoietic syndrome (HS) is a clinical diagnosis assigned to people who present with ≥ 1 new-onset cytopenias in the setting of acute radiation exposure. The World Health Organization convened a panel of experts to evaluate the evidence and develop recommendations for medical countermeasures for the management of HS in a hypothetical scenario involving the hospitalization of 100 to 200 individuals exposed to radiation. The objective of this consultancy was to develop recommendations for treatment of the HS based upon the quality of evidence.

Conclusions: Assessment of therapeutic interventions for HS in humans exposed to nontherapeutic radiation is difficult because of the limits in the evidence.

(Disaster Med Public Health Prep. 2011;5:202-212)