REVIEW ARTICLE

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

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## ABSTRACT

**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.

**Methods:** English-language articles were identified in MEDLINE and PubMed. Reference lists of retrieved articles were distributed to panel members before the meeting and updated during the meeting. Published case series and case reports of individuals with HS, published randomized controlled trials of relevant interventions used to treat nonirradiated individuals, reports of studies in irradiated animals, and prior recommendations of subject matter experts were selected. Studies were extracted using the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. In cases in which data were limited or incomplete, a narrative review of the observations was made. No randomized controlled trials of medical countermeasures have been completed for individuals with radiation-associated HS. The use of GRADE analysis of countermeasures for injury to hematopoietic tissue was restricted by the lack of comparator groups in humans. Reliance on data generated in nonirradiated humans and experimental animals was necessary.

**Results:** Based upon GRADE analysis and narrative review, a strong recommendation was made for the administration of granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor and a weak recommendation was made for the use of erythropoiesis-stimulating agents or hematopoietic stem cell transplantation.

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

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

**Key Words:** countermeasures for ARS, cytokines and radiation injury, transplantation for ARS, acute radiation syndrome management, hematopoietic syndrome management

Hematopoietic syndrome (HS) is a clinical diagnosis assigned to individuals who present with ≥1 new-onset cytopenias in the setting of whole-body or significant partial-body acute radiation exposure. The severity of lymphopenia and thrombocytopenia correlate in general with cumulative radiation dose and dose rate.[1] The rate of decline in absolute lymphocyte count correlates closely with dose and dose rate, and has been used as a surrogate marker for whole-body dose.[2,3] The primary causes of HS are radiation-induced suppression of mitosis in hematopoietic stem/progenitor cells and their progeny, resulting in hypocellularity and aplasia of the bone marrow and apoptosis in lymphocytes and other hematopoietic cells.

Although guidelines have been proposed to aid clinicians in the evaluation, triage, and/or medical management of victims of acute radiation injury,[4,5] the level of evidence supporting the current recommendations has not been evaluated. The World Health Organization (WHO) convened a panel of experts in Geneva, Switzerland, from March 16 to 18, 2009, to develop a har-



https://doi.org/10.1001/dmp.2011.68 Published online by Cambridge University Press

monized approach to the medical management of acute radiation exposure. Among their considerations was the evidence supporting the clinical management of HS.[6,7] Using the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for evaluating evidence supporting clinical guidelines,[8] the consultation group weighted the available evidence supporting the use of cytokines, hematopoietic stem cell transplantation, or both in the management of HS.

## METHODS

Participants in the consultancy were selected based upon their established expertise in the field. They were asked to consider and respond to a virtual scenario in which 100 to 200 victims required hospitalization. English language references were identified by each consultant before the meeting. All of the references were provided to the WHO and were made available to conferees. At the time of the meeting, additional English-language articles were identified in MEDLINE and PubMed from inception to the time of the consultancy. Search terms included *radiation* or *radiation toxicity* or *ionizing radiation and therapy or treatment* or *cytokines* or *transplantation* or *hematopoietic system*. Publications included case series, individual case reports of humans who were accidentally exposed to ionizing radiation, randomized control trials and cohort studies of humans who received therapeutic radiation or who may not have been exposed to radiation but who received the indicated treatment, reports of experimental studies in irradiated animals, and prior publications of recommendations of other consensus groups. Reference lists and references were distributed periodically throughout the meeting, as specific topics were raised for discussion.

Questions on the clinical management of HS were framed in the PICO format (patient problem, intervention, comparison, and outcome).[9] To assess the quality of the evidence objectively, drafts of GRADE evidence profiles were prepared, according to WHO recommendations for guideline development.[8] Letter assignments (A, B, C, and D) were made based upon the level of certainty that the magnitudes of benefits and harms of an intervention are known (Table 1 of the accompanying article by the same authors). Ranking the evidence with this tool was discussed and clarified by an expert (H.S.) on the GRADE approach.[10,11] Criteria included study design, study limitations, consistency rate across studies, directness or generalizability of study results, bias, dose-response gradient, and confounding variables. A single individual (R.N.G.) entered all of the data, and the subsequent findings were reviewed for accuracy by a subgroup of conferees (N.D., Z.C., R.S., J.A., and V.M.) in advance of consideration by the entire consultation group. All of the consultants were asked to make final comments before scoring the strength of each recommendation. A final consensus ranking of recommendations was made by e-mail to all of the conferees.

Strong or weak recommendations for the use of hematopoietic cytokines/growth factors or stem cell transplantation were made based upon the balance between desirable and undesirable consequences of alternative treatment strategies, the quality of the evidence, uncertainty about or variability in values and preferences, and impact on resource utilization. A numerical score was used to gauge the strength of recommendations (see the accompanying article by the same authors). These recommendations included one favoring a practice having a high certainty of substantial net benefit (1a) or a practice having a moderate certainty of moderate net benefit (1b). A recommendation against a practice was made when the practice was believed to have a moderate or high certainty of no net benefit (2a) or to have a moderate or high certainty of a small net benefit (2b).

## RESULTS

### Rationale for Cytokine Administration

Hematopoietic cytokines such as granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) have been used since the 1980s to treat radiation-associated cytopenias.[12] Although their use in radiation accident victims has been recommended by 2 expert groups,[4,5] the quality of the evidence supporting this recommendation is highly variable.

Clinical trial data supporting the use of cytokine efficacy in the treatment of humans with accidental radiation-induced hematopoietic stem/progenitor cell injury is not robust; additional evidence comes from studies in experimental animals. The administration of G-CSF, GM-CSF, erythropoiesis-stimulating agents (ESAs), and/or thrombopoietin-receptor agonists after exposure to ionizing radiation appears to significantly increase circulating blood counts in humans or nonhuman primates[12-15]; however, the lack of a human control group (eg, patients not receiving cytokine treatment) limits interpretation of these results.[16] Spontaneous recovery of blood counts occurred several weeks after the appearance of severe cytopenias in humans with HS, even in the absence of cytokine therapy.[17]

In an effort to justify the use and efficacy of cytokines in treating HS, researchers have used animal models. Based on the scientific literature suggesting a beneficial effect in the treatment of HS and the evidence of efficacy of cytokines in chemotherapy, a consensus has emerged that it is not ethically justifiable to conduct a placebo-controlled trial of cytokines in human victims of radiation sickness. In light of this lack of clinical equipoise, the best-available scientific evidence comes (and may continue to come) from animal-based experiments. Survival benefits observed in irradiated rhesus macaques and canines receiving G-CSF, GM-CSF, pegylated G-CSF thrombopoietin[13,18,19] support continued use of cytokines in humans exposed to high-dose ionizing radiation.

### Analysis of Cytokine Effects Using GRADE

In reviewing the evidence of hematological system injury, we found 5 reported accidents (Goiãnia, Brazil; Tokai-mura, Japan; Henan Province, China; Istanbul, Turkey; and Gilan, Iran), that enabled the establishment of bone marrow failure,



https://doi.org/10.1001/dmp.2011.68 Published online by Cambridge University Press

the documentation of cytokine use, and the demonstration of effect on the hematological system. Table 1 provides a summary of an analysis of the evidence. Table 2 is a complete GRADE analysis of the effects of cytokines on overall survival among individuals with cytopenias after exposure to ionizing radiation. Among these accidents, 18 cases of cytokine use were reported.[12,20-24] Eight patients received G-CSF and 10 received GM-CSF (Table 1).

Among the data reported from the Goiãnia accident, 2 patients experienced spontaneous reversal of leukopenia by 35 days postexposure to 6.2 or 7.1 Gy, and 8 individuals demonstrated persistent leukopenia for 24 to 47 days, and GM-CSF therapy was initiated at this time. Four of the individuals treated with cytokines (radiation doses of 2.5-4.4 Gy) survived and recovered from leukopenias. Four of the treated individuals (doses of 4.0-6.0 Gy received) died of Gram-negative sepsis and/or hemorrhagic complications, 3 of whom experienced minimal increase in their white blood cell count (Table 2). Four of the 6 patients from the Tokai-mura accident (1 patient) and the Henan Province accident (3 patients) were evaluable by GRADE, and all of them demonstrated improvement in absolute neutrophil count (Table 2).

In the 5 nuclear accidents, among the patients whose exposure dose was >5 Gy, 1 of 3 patients treated with cytokines survived. At exposures <5 Gy, 14 of 15 patients survived. The consultation group interpreted this observational finding as suggesting a possible benefit to myelopoiesis used in patients with exposure doses <5 Gy, when the only likely organ-critical failure is the hematopoietic system.

In assessing the effectiveness of cytokines, the GRADE analysis was severely restricted by our failure to identify any true control or comparator groups. Descriptive studies like these that do not have an appropriate, contemporaneous comparison group allow assessment of hypotheses for possible associations but not robust assessments of causality.[25] Randomized, appropriately designed, and powered studies are much more useful in studying causality.[25] In this case, a temporal association of cytokine administration followed by myeloid recovery should not be inferred as strong evidence of causality.[26]

## Rationale for Stem Cell Transplantation

Hematopoietic stem/progenitor cells of the bone marrow undergo mitotic death after exposure to ionizing radiation, with a $D_o$ (the radiation dose that reduces survival to $e^{-1}$ or 0.37 of its previous value on the exponential portion of the survival curve) for human marrow colony-forming units granulocyte-macrophage of $1.02 \pm 0.05$ at a dose rate of 2 Gy/min[27] and for human peripheral blood total colony-forming cells of $1.18 \pm 0.24$ at a dose rate of

## TABLE 1

**Among Individuals With Refractory Bone Marrow Failure After Exposure to Ionizing Radiation, Do Cytokines (G-CSF or GM-CSF) vs No Such Therapy Affect Overall Survival?[12,20-26]**

| Quality Assessment | | | | | | | Summary of Findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. Patients | | | | |
| No. Studies, Patients | Design | Study Limitations | Consistency | Directness | Precision | Other Considerations | No. Treated With Cytokines/ Patients | No. Not Treated With Cytokines/ Patients | Effect* | Quality | Importance |
| 5 studies, 20 patients identified with refractory bone marrow failure (among a total of 31 patients reported with ionising radiation injury in these studies†) 18 patients treated primarily with cytokines‡ | Observational studies | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Strong temporal association between intervention with cytokines and bone marrow recovery in 14/15 patients in whom bone marrow recovery was observed† | 18/20 (90%) | 2/20 (10%) | Bone marrow recovery observed in 15/17 patients treated with cytokines (88%) Survival reported in 14/17 patients treated with cytokines (82%); outcome data available for only 17/18 patients‡ | ⊕⊕⊕○ Moderate | Critical§ |

*Relative risk not calculable with the available data.

†The group of patients not requiring treatment for bone marrow failure includes 2 patients from the Goiãnia accident with dose exposures of 6.2 and 7.0 Gy in whom spontaneous late recovery of bone marrow occurred and hence did not require consideration for cytokine therapy; spontaneous recovery in other cases reported in these studies were among patients who had received absorbed doses of radiation in the range of .6 to 2.9 Gy.

‡Two patients from the Tokai-mura accident with bone marrow failure were managed primarily with hematopoetic stem cell transplants.

§Outcome of intervention has great clinical significance (survival vs death) because refractory bone marrow failure is considered to be inevitably lethal.



https://doi.org/10.1001/dmp.2011.68 Published online by Cambridge University Press

0.8 Gy/min.[28] This particular in vitro measure of sensitivity to radiation correlates with the appearance of the HS that occurs in individuals whose partial-body or whole-body radiation exposure exceeds approximately 1 Gy.[7,29] The clinical correlate of this laboratory observation is the significantly diminished capacity of hematopoietic stem/progenitor

## TABLE 2

**Analysis of Studies Included in the GRADE Profile Question: Among Individuals With Cytopenias After Exposure to Ionizing Radiation, Do Cytokines (G-CSF or GM-CSF) vs No Such Therapy Affect Overall Survival?**

| Accident | Study Design Data Extracted From | Estimated Whole Body Absorbed Doses | Cytokine Treatment | Outcome in Patients Treated With Cytokines | Outcome in Patients Not Treated With Cytokine | Other Considerations and Limitations | Summary of Findings | Effects | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| Goiânia, Brazil, (2007)[12,21]<br>Mishandling of an abandoned caesium-137 teletherapy unit | Case series report of treatment of 14 patients with bone marrow failure | 6.2 Gy†<br>2.7 Gy<br>7.0 Gy†<br>6.0 Gy<br>4.5 Gy<br>5.5 Gy<br>5.3 Gy<br>4.3 Gy<br>2.9 Gy<br>4.4 Gy<br>2.9 Gy*<br>1.3 Gy*<br>1.6 Gy*<br>1.0 Gy* | GM-CSF | 8 patients with absorbed doses in range of 2.7-6.0 Gy, who developed bone marrow failure, were treated with cytokines; data was available to evaluate outcome on 7 of these cases<br>5/7 patients treated with cytokines had evidence of hematological recovery temporally associated with cytokine therapy<br>4/5 patients with absorbed doses in the range 2.7-4.4 Gy had a good response to cytokine therapy and survived<br>2/7 patients with absorbed doses of 4.0 and 6.0 Gy had poor or no hematological response to cytokine therapy and subsequently died | 2 patients with absorbed doses of 6.2 and 7.0 Gy were not treated with cytokines; both patients had spontaneous recovery of bone marrow by day 35 and were not considered for treatment<br>4 patients with absorbed doses in the range 1.0-2.9 Gy suffered minor hematological impairment requiring treatment | 4 patients who were treated with cytokines were colonized with gram-negative bacteria before GM-CSF therapy was commenced. All 4 of these patients died; 2 from septicemia and 2 from diffuse hemmorhage<br>Internal radiological contamination present in some patients as a complicating factor; one unevaluable patient was treated with cytokines and died | Good hematological response to treatment with GM-CSF was reported in 5/7 patients who received dose of radiation in range of 2.7-6.0 Gy<br>Poor or no response was seen in 2/7 patients<br>Death occurred in all cases where gram-negative colonization was present before cytokine therapy was commenced, whether hematological recovery was observed, or not<br>Spontaneous recovery of bone marrow may still occur in patients with relatively high doses of radiation | Hematological response recorded and concordant with GM-CSF therapy in 5/7 patients with dose exposure of 2.7-6.0 Gy | Moderate quality<br>Observational study where clinical outcome is clearly documented and both the hematological recovery and completed outcome also include evidence related to success of cytokine therapy where gram-negative septicaemia is present before cytokine therapy is initiated | Critical |
| Tokai-mura, Japan (1999)[22]<br>Nuclear criticality accident<br>Mixed gamma (γ) and neutron irradiation | Case series report of treatment of 3 patients with bone marrow failure and other severe radiation injuries | Mixed 5.5 Gy neutrons 8.5 Gy gamma<br>2.9 Gy neutrons 4.5 Gy gamma<br>.81 Gy neutrons 1.3 Gy gamma | G-CSF | One patient who had received an absorbed dose of 0.81 Gy neutrons and 1.3 Gy gamma, and developed bone marrow failure, was treated with cytokines and had evidence of hematological recovery temporally associated with cytokine therapy | No untreated patients | Hematopoietic stem cell transplantation initially used in management of 2 patients who received the highest radiation doses and these cases have been excluded from GRADE evaluation<br>This was the only case series identified in the extant literature with mixed neutron and γ-irradiation injury | Good hematological response to treatment with G-CSF in patient who did not receive hematopoietic stem cell transplantation | Hematological response recorded and concordant with G-CSF therapy in 1/1 patient with dose exposure of .81 Gy neutrons and 1.3 Gy γ | Low quality<br>Observational study where the case reporting on the uncomplicated use of cytokines is limited to a single patient | Important |

*(continued)*



https://doi.org/10.1001/dmp.2011.68 Published online by Cambridge University Press

cells to proliferate in vivo after a whole-body dose exceeding 2 to 3 Gy.

Depending on the dose, dose rate, and radiation quality factor, various degrees of pancytopenia develop over several weeks after whole-body or significant partial-body exposure.[4,6,30] Hypocellularity and aplasia of the bone marrow may occur at doses >3 Gy.[4,6,30,31] Factors that may exacerbate the effects of radiation include a patient's age, underlying state of health, and overall nutritional status.

Hematopoietic stem/progenitor cell therapy has been recommended for patients with complete aplasia of the bone marrow, as assessed by bone marrow biopsies taken from 2 noncontiguous sites.[4,5] Such individuals would be expected to have third- or fourth-degree hematopoietic toxicity (Table 3).

## Analysis of the Effects of Bone Marrow Transplantation Using GRADE

A crude meta-analysis of 3 reported incidents in which bone marrow transplantation was used to treat radiation-induced marrow failure was performed. Table 4 provides a summary of this analysis. Table 5 presents a complete GRADE analysis of the question of the impact of bone marrow transplantation on overall survival among individuals with bone marrow failure after exposure to ionizing radiation. In these reports,[32-35] some of which

## TABLE 2

**Analysis of Studies Included in the GRADE Profile Question: Among Individuals With Cytopenias After Exposure to Ionizing Radiation, Do Cytokines (G-CSF or GM-CSF) vs No Such Therapy Affect Overall Survival? (continued)**

| Accident | Study Design Data Extracted From | Estimated Whole Body Absorbed Doses | Cytokine Treatment | Outcome in Patients Treated With Cytokines | Outcome in Patients Not Treated With Cytokine | Other Considerations and Limitations | Summary of Findings | Effects | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| Henan Province, China (1999)[23] Accidental exposure to high-dose cobalt-60 radiation source | Case series report of treatment of 3 patients with bone marrow failure | 6.1 Gy 3.4 Gy 2.4 Gy | GM-CSF (patient who received 6.1 Gy was treated with both GM-CSF and EPO) | 3/3 patients with absorbed doses in the range 2.4-6.1 Gy, who developed bone marrow failure, were treated with cytokines had evidence of hematological recovery temporally associated with cytokine therapy | No untreated patients | Early recognition of radiation injury and early prompt treatment including strict infection control and cytokine therapy | Good hematological response to treatment with GM-CSF/ GM-CSF/epoetin | Hematological response recorded and concordant with G-CSF therapy in 3/3 patients with dose exposure of 2.4-6.1 Gy | Moderate quality Observational study enhanced by good assessment of dose exposure and measurement of hematological parameters with clear evidence of time-related response relation | Critical |
| Gilan, Islamic Republic of Iran (1996)[24] Accidental exposure of workers to an Iridium-192 industrial radiography source | IAEA accident report detailing single irradiated patient affected | 2.5-3.5 Gy (dose range estimate for single patient) | G-CSF | One patient, with an absorbed dose in the range of 2.5-3.5 Gy was treated with cytokines and had evidence of hematological recovery incidental with cytokine therapy | No untreated patients | Some uncertainty in dose received Distribution of radiation dose was non-uniform | Cytokine therapy may not have contributed to marrow recovery because of its relatively late initiation, and evidence that bone marrow recovery may already have been underway | The physiological effect of cytokine therapy demonstrated in a patient exposed to an absorbed dose of 2.5-3.5 Gy; however, as there is a possibility that spontaneous recovery of the bone marrow was already occurring, the evidence from this case may, therefore, be of limited utility in evidencing the value of cytokine therapy | Low quality Observational study of a single case where the cytokine therapy may not have been necessary for hematological recovery | Not important |

*(continued)*



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predate the use of cytokines, survival appeared not to rely on transplantation, and may have been affected adversely by transplantation.

Stratification of the results from the Chernobyl study[33] suggests that survival is more likely among individuals receiving <9 Gy and no bone marrow transplant. Nevertheless, the data are too restrictive to allow definitive statistical analysis. Survival in 2 additional patients (one receiving a peripheral blood transplant and the other receiving a cord blood transplant) from the Tokaimura accident was possibly longer than predicted by the estimated whole-body radiation dose.[36] These individuals also received concurrent cytokine therapy, and comparators were not available. Data are insufficient to determine the impact of genetically identical bone marrow transplantation on outcomes.

In summary, the data available from these reports strongly suggest that the effect of hematopoietic stem/progenitor cell transplantation is unproven as initial therapy for HS after irradiation.

## RECOMMENDATIONS

The consultation group strongly considered the GRADE evidence profiles for cytokine administration and bone marrow transplantation in developing recommendations for the management of HS. The group also derived recommendations in part from results of these therapies in controlled animal trials. During the deliberation process, guidelines provided by expert consensus groups and by national and international societies also were considered, reviewed, and discussed.

## TABLE 2

**Analysis of Studies Included in the GRADE Profile Question: Among Individuals With Cytopenias After Exposure to Ionizing Radiation, Do Cytokines (G-CSF or GM-CSF) vs No Such Therapy Affect Overall Survival? (continued)**

| Accident | Study Design Data Extracted From | Estimated Whole Body Absorbed Doses | Cytokine Treatment | Outcome in Patients Treated With Cytokines | Outcome in Patients Not Treated With Cytokine | Other Considerations and Limitations | Summary of Findings | Effects | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| Istanbul, Turkey (1998)[25] Mishandling of a disused cobalt-60 teletherapy unit teletherapy unit | IAEA accident report detailing treatment of 10 irradiated patients, 5 of whom suffered bone marrow failure | Cases reported with bone marrow failure 2.2 Gy 2.3 Gy 3.1 Gy 2.5 Gy 2.5 Gy | G-CSF | 5 patients treated with absorbed doses in the range 2.2-3.1 Gy were treated with cytokines and had evidence of hematological recovery temporally associated with cytokine therapy | 5 other patients were identified in the accident report with absorbed doses of 0.6-1.8 Gy that did not have significant hematological impairment | Cytokine therapy commenced 4 wk after initial exposure of patients | Good hematological response to treatment with GM-CSF despite delay in initiation of treatment | Hematological response recorded and concordant with G-CSF therapy in 5/5 patients with dose exposure of 2.3-3.1 Gy | Moderate quality Observational study enhanced by good assessment of dose exposure and measurement of hematological parameters with clear evidence of time-related response relation | Critical |

G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony-stimulating factor; IAEA = International Atomic Energy Agency.

Principal criterion for inclusion: All of the studies were observational reports on the outcomes of the use of a cytokine in established refractory bone marrow failure using either G-CSF or GM-CSF. Additional criteria for exclusion: radiation exposure was in a nontherapeutic setting; reporting of the clinical details of the incident is in the public domain; radiation doses received were established with sufficient accuracy as to reliably attribute bone marrow injury to ionizing radiation exposure; reported cases had no other clinical reason to experience bone marrow injury; treatment did not include the use of complex mixtures of cytokines; outcome was not confounded by bone marrow grafting or the use of stem cells; report contained sufficient clinical information to establish clear evidence of bone marrow injury; and report contained sufficient clinical information to establish clear evidence of consequent effects on bone marrow.

*Patients with minor hematological impairment not requiring treatment.

†Patients whose bone marrow recovered spontaneously.

## TABLE 3

**Levels of Hematopoietic Toxicity[1]**

| Symptom or Sign | Degree 1 | Degree 2 | Degree 3 | Degree 4 |
|---|---|---|---|---|
| Lymphocyte changes* | $\geq 1.5 \times 10^9$ cells/L | $1\text{-}1.5 \times 10^9$ cells/L | $.5\text{-}1 \times 10^9$ cells/L | $<.5 \times 10^9$ cells/L |
| Granulocyte changes† | $\geq 2 \times 10^9$ cells/L | $1\text{-}2 \times 10^9$ cells/L | $.5\text{-}1 \times 10^9$ cells/L | $<.5 \times 10^9$ cells/L |
| Thrombocyte changes‡ | $\geq 100 \times 10^9$ cells/L | $50\text{-}100 \times 10^9$ cells/L | $20\text{-}50 \times 10^9$ cells/L | $<20 \times 10^9$ cells/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 $1.4\text{-}3.5 \times 10^9$ cells/L.

†Reference value $4\text{-}9 \times 10^9$ cells/L.

‡Reference value $140\text{-}400 \times 10^9$ cells/L.





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Although the evidence for cytokine administration from radiation incident reports alone is weak, results are remarkably consistent from controlled animal trials[13,18,37,38] and reports recommending the use of CSF in nonirradiated (eg, chemotherapy treated) patients with malignancy, as recommended by the American Society of Clinical Oncology,[39] by the European Society of Medical Oncology,[40] and by consensus groups.[4,5,29] The consistency of the observation that cytokines successfully treat hematological injury in animal models and in humans with hematological deficits of nonradiation origin, together with the relatively limited drug-related toxicity reported for certain cytokines, leads to a strong recommendation that these cytokines should be used in the management of radiation-induced hematotopoietic system injury (Table 6).

Health care providers should consider initiating cytokine therapy for exposures of ≥2 Gy and/or a significant decrease in the absolute lymphocyte count, or when it is anticipated that neutropenia of $<.5 \times 10^9$ cells per liter will persist for ≥7 days. It is recommended that cytokine therapy with G-CSF or GM-CSF be initiated within 24 hours of exposure. Pegylated G-CSF may be used as an alternative to G-CSF. Patients should continue to receive treatment until their absolute neutrophil count reaches and maintains a level $>1.0 \times 10^9$ cells per liter in the absence of active infection. Those with infection should be treated with cytokines, according to the guidelines published by infectious disease societies, including the Infectious Diseases Society of America.[41]

Individuals with prolonged anemia, a significant decline in hemoglobin concentration, or both may be candidates for treatment with erythropoietin. In contrast to the relatively short life span of myeloid cells and platelets (<10 days), the life span of erythrocytes is approximately 120 days. Experiencing a response to erythropoietin will take weeks rather than days. Consideration should be given to the administration of oral iron supplementation in individuals receiving ESAs. ESAs may be considered in the lowest dosage that induces a sufficiently high hemoglobin level to render blood transfusion unnecessary (ie, 9-10 g/dL), although a higher level of hemoglobin may be reasonably targeted on a case-by-case basis. Strong caveats recommending specific indications for the use of ESAs are incorporated in a "black box" warning by the US Food and Drug Administration (FDA).[42] The initial dose of ESAs should follow the recommendations of the FDA, the the European Medicines Agency, or other relevant regulatory authorities, as provided in the manufacturer's labeling. Dosing is based on a patient's hemoglobin level at the initiation of therapy, his or her target hemoglobin level, the observed rate of increase in hemoglobin level, and individual clinical circumstances. Finding few published reports in humans with nonimmunological thrombocytopenia or exposure to radiation, the consultancy group makes no recommendation regarding the use of second-generation thrombopoietic growth factors.

Because patients with severe hematopoietic injury may recover, either spontaneously or after G-CSF treatment alone,

## TABLE 4

**Among Individuals With Bone Marrow Failure After Exposure to Ionizing Radiation, Does Bone Marrow Transplantation vs No Transplantation Affect Overall Survival?[32-35]**

| Quality Assessment | | | | | | | Summary of Findings: No. Patients | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. Studies (No. participants) | Design | Study limitations | Consistency | Directness | Precision | Other Considerations | No. Treated With Transplantation/ Participants (%) | No. Not Treated With Transplantation/ Participants (%) | Effect*† | Quality | Importance |
| 3 (19 graft recipients reported in 3 studies; outcome in 14 unmatched comparators available in 1 study‡) | 3 observational studies; 1 of these studies reports some data on an unmatched comparative population | No serious study limitations | Large range of dose exposures in which 7/19 cases may not have been exposed to radiation dose associated with inevitable bone marrow failure | No unequivocal evidence of engraftment or graft failure reported in 6 treated cases (5/6 of whom survived) from 1 study§ | No serious imprecision | Survival outcome strongly influenced by severity of damage to other organs and effects of treatment to prevent graft rejection and development of graft-vs-host disease | 19/33 (58) | 14/33 (42) | Survival observed in 2/13 (15%) treated patients Survival observed in 6/14 (43%) patients not treated | ⊕⊕⊕○ Moderate | Critical‖ |

*Relative risk not calculable with available data.
†Effect reported only for data aggregated for Chernobyl studies because recruitment/dose exposure (evidence of bone marrow failure and/or dose exposure not inevitably associated with bone).
‡Criticality accident, Chernobyl, former Soviet Union[34] (marrow failure) and/or endpoint (engraftment) not clearly documented or proven.
§Criticality accident, Boris Kidrich Institute, Vinca, Yugoslavia.[35]
‖Outcome of intervention has great clinical significance (survival vs death).

# TABLE 5

**Analysis of Studies Included in the GRADE Profile Question: Among Individuals With Bone Marrow Failure After Exposure to Ionizing Radiation, Does Bone Marrow Transplantation vs No Transplantation Affect Overall Survival?**

| Accident | Design | Estimated Whole-Body Doses Received | Bone Marrow Transplantation Technique Used | Outcome in Patients Treated With Bone Marrow Transplantation | Outcome in Patients Not Treated With Bone Marrow Transplantation | Other Considerations and Limitations | Summary of Findings | Effects | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| Vinca, Yugoslavia,[35] criticality accident during an experiment at the Boris Kidrich Institute | Case series report of treatment of 5 patients with bone marrow failure | Not known with a reasonable degree of precision<br>Original clinical case report gave following ranges (in Sv) for the total doses received: 10-12, 7-10, 7-10, 7-10, 6-8, and 3-5<br>Reconstruction of the incident provides evidence that actual doses received were lower than initial estimates<br>IAEA *Vinca Dosimetry Experiment*[35] suggested following dose exposures (in Gy): 4.36, 4.26, 4.19, 4.14, 3.23, and 2.07 (reports quoted gave these values in rad/rem and the conversion factors of 1Sv 100 rem and 1 Gy = 100 rad were used) | HLA-unmatched bone marrow transplants | 4/5 patients survived with good hematological recovery | No untreated patients | No evidence of engraftment, and hematological recovery may have been caused by either spontaneous recovery of patient's own bone marrow or engraftment | Case series in which 4/5 patients survived with good hematological recovery in an incident in which the dose exposure is uncertain and no markers of engraftment are available to identify whether HLA-unmatched bone marrow transplantation was responsible for survival of those treated | 4/5 exposed people who survived after exposure to doses of radiation that may not have inevitably produced lethal bone marrow damage whose treatment included bone marrow grafting | Low quality: significant uncertainty of dose exposure<br>No evaluation of severity of hematological injury to establish need for treatment<br>No clear evaluation of an engraftment endpoint to demonstrate unequivocally the role of bone marrow transplantation in their treatment | Limited importance |
| Pittsburgh, PA,[36] industrial linear accelerator accident | Case report of treatment of 1 patient with bone marrow failure | 3 patients affected, only 1 reported to have received a radiation dose likely to have caused severe hematological injury, which was estimated as 6.0 Sv; dose was heterogeneous (feet 27 Sv and hands 59 Sv) | Bone marrow transplant from genetically identical twin | 1/1 patient survived with good hematological recovery | No untreated patients | Evidence of complete bone marrow destruction not established<br>Dose significantly heterogeneous<br>Graft taken from genetically identical twin and no definitive marker of engraftment therefore available | Single case in which 1/1 patients survived with good hematological recovery following transplantation from a genetically identical twin<br>Uncertain evidence of degree of bone marrow failure and no evidence of engraftment | 1/1 patients exposed to radiation dose that may be expected to impart significant bone marrow impairment survived whose treatment included bone marrow graft | Low quality: single case with significantly heterogeneous dose and uncertain evidence of bone marrow failure<br>Not possible to identify engraftment endpoint to demonstrate unequivocally role of bone marrow transplantation in treatment | Limited importance |

*(continued)*



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## TABLE 5

**Analysis of Studies Included in the GRADE Profile Question: Among Individuals With Bone Marrow Failure After Exposure to Ionizing Radiation, Does Bone Marrow Transplantation vs No Transplantation Affect Overall Survival? (continued)**

| Accident | Design | Estimated Whole-Body Doses Received | Bone Marrow Transplantation Technique Used | Outcome in Patients Treated With Bone Marrow Transplantation | Outcome in Patients Not Treated With Bone Marrow Transplantation | Other Considerations and Limitations | Summary of Findings | Effects | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| Chernobyl, former Soviet Union,[34] criticality accident with significant release of radioactive materials into environment from an industrial electricity-generating reactor | Case series report of treatment of 13 patients with bone marrow failure treated with bone marrow grafting; limited reporting of outcome in 14 cases of similar dose exposure that did not receive transplants | Biological marker estimated doses (in Gy): 6.6, 9.2, 12.1, 11.9, 4.4, 5.2, 9.6, 5.6, 10.2, 13.4, 8.3, 6.4, and 8.7 | Histocompatibility (H = haplotype; H1 = haplotype and 1 locus; Id = identical): H1 (father), Id (brother), Id (sister), H1 (mother), H1 (sister), Id (brother), Id (brother), H (sister), H (mother), H (brother), Id/H1 (brother),* Id (sister), H (sister) | Outcomes reported at day 1187 after accident: died (burns), died (GI /burns/ pneumonitis), died (GI/burns), died (burns), died (ARF/ ARDS), died (GvH/ infection), died (GI/ burns), survived, died (GvH/ interstitial pneumonia), died (burns/GI complications/ interstitial pneumonia), died (GvH/ hepatic failure/ interstitial pneumonia), died (GvH/infection/ ARF), survived, 2/13 survived who had dose exposures of 5.6 and 8.7 Gy<br>Survival stratified by dose in patients who received grafts was ≥9 Gy 0/6, <9 Gy 2/7 | 15 patients were selected for transplantation with criteria of dose ≥6 Gy, full or partial HLA-typed donor availability, predicted absence of irreversible lethal damage to other organs<br>No sib/parent donor could be found for 2 cases; HLA-matched nonfamilial donors were found for these cases; outcomesof these cases were 1 case subsequently developed organ damage judged to be likely lethal; 1 case refused consent for transplantation; limited data reported on 14 people who did not receive transplants with similar dose exposure<br>Survival stratified by dose in patients who did not receive grafts was ≥9 Gy 0/6, <9 Gy 6/8 | Radiation injury judged to be relatively homogeneous in all cases<br>Severity of other organ injuries dominant as cause of death<br>Initial engraftment identified in 8 cases, of whom 7/8 survived for at least 14 d after transplantation<br>Graft-vs-host disease identified in 4/8 of cases in which initial engraftment identified<br>Interstitial pneumonitis identified in 4/13 cases in which grafting undertaken<br>Engraftment probably transient in both survivors | Case series in which 2/13 patients survived with good hematological recovery after transplantation<br>Evidence of bone marrow failure is good<br>Grafting from donors with partial or complete HLA typing was undertaken<br>Of the 2 survivors, engraftment was probably transient<br>Adverse effects of adjunctive treatment to enable grafting to occur are present in 5/11 patients who died (GvH/interstitial pneumonitis, or both)<br>Cause of death in all cases complicated by significant damage to other organs | 2/13 patients exposed to a dose of radiation that may be expected to impart significant bone marrow impairment survived whose treatment included bone marrow grafting<br>6/14 patients exposed to dose of radiation that may be expected to impart significant bone marrow impairment survived whose treatment did not include bone marrow grafting<br>Adverse effects of treatment potentially significant in 5/11 deaths | Moderate quality: reporting of intervention group is to a high standard and all relevant information can be elicited<br>Reporting of a control group is poor with no matching data available<br>Negative effects of intervention significantly intermingled with organ damage from radiation | Critical |

ARF-ARDS = adult respiratory distress syndrome/acute respiratory failure; GI = gastrointestinal; GvH = graft-vs-host disease; HLA = human leukocyte antigen. Principal criterion for inclusion: All studies with an observational outcome regarding the use of bone marrow transplantation in irradiated individuals with bone marrow failure. Additional criteria for exclusion: radiation exposure was in a nontherapeutic setting; reporting of the clinical details of the incident is in the public domain; reported cases had no other clinical reason to experience bone marrow injury; report contained sufficient clinical information to establish clear evidence of bone marrow injury; report contained sufficient clinical information to establish clear evidence of consequent survival; and information on the radiation doses received was available.

*Unresolved laboratory testing disparity.



https://doi.org/10.1001/dmp.2011.68 Published online by Cambridge University Press

## TABLE 6

**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<.500 × $10^9$ cells/L | Strong (B-1a) |
| Administer ESAs when prolonged anemia is present to avoid need for red blood cell infusion | Weak (C-1b) |
| Administer hematopoietic stem cells after failure of 2-3 wk of cytokine treatment to induce recovery from marrow aplasia in absence of nonhematopoietic organ failure | Weak (D-1b) |

ANC=absolute neutrophil count; ESA=erythropoiesis-stimulating agents; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor.

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.

clinicians considering bone marrow transplantation are advised to adopt a wait-and-see approach with careful surveillance. Stem/progenitor cell replacement therapy should not be administered until there is a documented lack of spontaneous recovery and/or lack of response following 2 to 3 weeks of cytokine treatment. Survival outcomes have been poor among patients who have received transplants who also have radiation burns, gastrointestinal syndrome, infection, adult respiratory distress syndrome, and/or renal insufficiency[32-36]; therefore, it has been recommended that hematopoietic stem/progenitor cell therapy not be used for patients with aplasia and significant injury to another organ system.[4,7,29,43,44] With these caveats in mind, the consulting group makes a weak recommendation for the administration of allogeneic hematopoietic stem/progenitor cells from the bone marrow, peripheral blood, or cord blood of patients who are unresponsive to cytokine therapy and in whom there is no significant injury to a nonhemopoietic organ system (Table 6).

## CONCLUSIONS

The WHO panel of experts used the GRADE tool to extract and analyze data from reports of cytokine administration and/or bone marrow transplantation in individuals with HS after exposure to ionizing radiation. The lack of comparator groups in humans restricts these analyses. Nevertheless, together with results of controlled trials in large animals and clinical trials in nonirradiated humans, these analyses support the strong recommendation for G-CSF or GM-CSF administration and the weak recommendation for ESA or hematopoietic stem cell administration in humans with HS.

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Received for publication June 28, 2011; accepted August 30, 2011.

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**Author Disclosures:** Dr Weinstock has been a consultant to Genzyme and Novartis.

The other authors report no conflicts of interest.

**Acknowledgments:** Owing to their seminal contributions in the field of radiation biology and their pioneering approaches to treatment of victims of radiation injury, this consultancy report is dedicated to Theodor M. Fliedner and Angelina Guskova. The authors thank Makoto Akashi, Axel Bottger, Thierry de Revel, Patrick Gourmelon, Richard Hatchett, Mikhail Konchalovski, Ying Liu, Maria Julia Marinissen, Hilary Walker, Helmut Walerius, and Wei Zhang for participating in the consultancy and contributing to consensus building. The authors are grateful to the National Institute of Allergy and Infectious Diseases for providing financial support for this consultancy.

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