

Hematopoietic Recovery After 10-Gy Acute Total Body Radiation

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Considerable data suggest that very high doses of acute total body radiation destroy most hematopoietic stem cells and that recovery is possible only after a bone marrow transplant. We review data from a radiation accident victim exposed to about 10-Gy or more acute total body radiation. Total dose and uniformity of distribution were confirmed by physical measurements (paramagnetic resonance), computer simulation, and biologic dosimetry (granulocyte kinetics and cytogenetic abnormalities). Treatment consisted of supportive measures, transfusions, and hematopoietic growth factors (granulocyte-macrophage colony-stimulating factor and interleukin-3). Hematopoietic recovery occurred slowly. Granulocytes were detect-

able throughout the postexposure period, exceeding $0.5 \times 10^9/L$ by day 37. There was slower and incomplete recovery of red blood cells and platelets. Increases in blood cell production were paralleled by morphologic changes in bone marrow biopsies. Gastrointestinal toxicity was moderate. Death from a probable radiation pneumonitis infection occurred on day 130. These data indicate the possibility of hematopoietic recovery after approximately 10 Gy or more acute total body radiation without a transplant. They also suggest that lung rather than gastrointestinal toxicity may be dose-limiting under these circumstances.

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HEMATOPOIETIC CELLS are extremely sensitive to damage by ionizing radiations.¹⁻³ The 50% lethal dose (LD₅₀) to the bone marrow (BM) in humans is estimated to be 3 to 4 Gy. Damage to hematopoietic stem cells after doses exceeding 8 Gy is usually considered irreversible and hematopoietic recovery possible only after a bone marrow transplant. We present data indicating partial hematopoietic recovery after exposure to about 10-Gy or more acute total body radiation in a radiation accident victim treated with supportive measures, transfusions, and hematopoietic growth factors but no transplant.

PATIENT AND METHODS

Accident. A 34-year-old male operator of a ⁶⁰Co γ-radiation sterilization facility in Nieshvesh, Belarus entered the sterilization area when the ⁶⁰Co source (specific activity, 8×10^5 Ci) was exposed. He approached the source from an initial distance of 4 m, walking directly to a site about 0.5 m distant and facing it with his left side slightly anterior. At this point he realized the source was exposed and exited via the same route he entered. Total exposure time was estimated at 1 to 2 minutes, with more than 90% of this time spent approaching or departing from the source. The extremely wide field of the source (minimum 3 m at a distance of 0.5 m), distance from which the victim approached (4 m), and absence of any shielding in the room make it certain that exposure was relatively uniform and involved the whole body.

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Submitted March 18, 1993; accepted September 7, 1993.

Supported in part by grants from the Center for Advanced Studies in Leukemia and from Occidental Petroleum Foundation (Dr Ray Irani). R.P.G. is the Wald Foundation Scholar in Biomedical Communications.

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0006-4971/94/8302-0002\$3.00/0

Nausea and emesis occurred within 3 minutes of exiting the facility and continued for about 6 hours. Diarrhea occurred about 13 minutes later and was associated with headache, fatigue, fever (38.5°C), tachycardia, hypotension, and abdominal pain. Two hours postexposure, the white blood cell count (WBC) was $13.1 \times 10^9/L$ (11.9 granulocytes; 0.91 lymphocytes) and the platelet count was $180 \times 10^9/L$. Because the initial assessment indicated exposure to high-dose radiation, he was flown to a radiation emergency unit in Moscow, arriving within 15 hours of exposure. Additional details of the accident will be reported.

Dosimetry. Radiation dose and uniformity of distribution was determined by physical measurements, computer simulation, and biologic dosimetry.^{4,8}

Paramagnetic resonance (PMR) analysis of samples of dental enamel performed at laboratories in Russia and North America was consistent with a dose of 14.0 ± 0.7 Gy (SEM). Twelve samples of clothing obtained from 8 sites on the chest, back, and sides and from the 4 extremities showed a median dose of 15 ± 1.5 Gy. The highest measurement were recorded from the left anterior chest (18 Gy) and the lowest from the left posterior chest (12 Gy). Measurements of cloth from all 4 extremities exceeded 10 Gy. Similar studies were performed using 2 or more nail samples from the 4 extremities. All of these measurements exceeded 10 Gy.

Computer accident simulations were consistent with a dose of 12.5 Gy (95% confidence interval, 10 to 15 Gy).

Dose estimates were also made using dynamic biologic parameters.⁵⁻⁸ The dose estimate based on blood granulocyte kinetics was 9 to 11 Gy. Direct cytogenetic analysis of cultured blood lymphocytes suggested a dose of 9.6 to 11.7 Gy. The pooled biologic dose estimate based on previously published criteria was 9.9 Gy.⁸ These data are summarized in Table 1.

Hospital course and treatment. Admission physical exam was unremarkable save for mild diffuse hyperemia and parotid tenderness. The WBC was $12.6 \times 10^9/L$ (11.9 granulocytes and 0.3 lymphocytes) and the platelet count was $225 \times 10^9/L$. The hemoglobin level was 14.3 g/dL. Biochemical studies, including creatinine, bilirubin, and hepatic transaminases, were normal. The amylase level was 248 mg/h/L (normal, 16 to 30 mg/h/L).

Infection prophylaxis was begun with norfloxacin, trimethoprim-sulfamethoxazole, ketoconazole, acyclovir, intravenous Ig, and a laminar air flow protected environment. Red blood cells (RBCs) and platelet transfusions (radiated with 25 Gy) were administered to maintain a hemoglobin level greater than 10 g/dL and a platelets count greater than $20 \times 10^9/L$. Intravenous hyperalimentation was begun.

Because considerable experimental and clinical data in animals and humans suggest that at least some hematopoietic stem cells survive even very high doses of acute total body radiation,⁹⁻¹⁴ we decided to use molecularly cloned hematopoietic growth factors to

Table 1. Radiation Dosimetry

Technique	Source	Estimated Dose (Gy)	95% Confidence Interval (Gy)
PMR	Teeth	14.0 ± 0.7	12.6-15.4
	Clothes	15.0 ± 1.5	12.0-18.0
Computer	—	12.5	10.0-15.0
Biologic	Granulocytes	—	9.0-11.0
	Cytogenetics	—	9.6-11.7
	Pooled*	9.9	8.6-11.2

Abbreviation: PMR, paramagnetic resonance.

* See Baranov et al.⁸

accelerate bone marrow recovery. Granulocyte-macrophage colony-stimulating factor (GM-CSF; Sandoz Pharmaceuticals, Basel, Switzerland) was administered at a dose of 250 µg/m²/d from day 3 to 6 and from day 16 to 39. Interleukin-3 (IL-3; Sandoz Pharmaceuticals) was administered at the same dose from days 8 to 31. Both were infused in a volume of 250 mL over 2 hours.

Six days after exposure, the subject developed bloody diarrhea with stool volumes ranging between 0.2 and 1.3 L per day (typically 0.5 L per day). Melena resolved after 1 week, but diarrhea persisted until 50 days postexposure. The results of biochemical studies, including creatinine, bilirubin, and hepatic transaminases, remained normal. The amylase level decreased to normal by day 8.

A fever exceeding 38.5°C developed 2 days postexposure concomitant with cutaneous activation of latent herpes simplex infection. Treatment was begun with azlocillin and cefepazone. Low-dose amphotericin-B was started shortly thereafter because of persisting fever. On day 38, an X-ray showed focal lesions in both lungs. Bronchoscopy with alveolar lavage and transbronchial biopsy as well as percutaneous needle biopsy showed no bacterial, fungal, or viral pathogens on culture or histologic examination.

Radiation dermatitis developed on day 15. This affected all face and body areas, but was greatest on the left side. It persisted until day 70, when it gradually resolved.

Between days 75 and 100, the subject was afebrile, lung abnormalities were stable, and transfusion requirements decreased. Parenteral nutrition, antibiotics, and amphotericin were stopped.

On day 100, the left lung lesions increased in size. An open biopsy showed areas of focal and diffuse fibrosis but without evidence of infection. On day 104, the subject developed acute respiratory distress syndrome, dying on day 113 of respiratory failure.

RESULTS

Hematologic recovery. Sequential hematologic studies are summarized in Fig 1. The number of granulocytes fell rapidly, decreasing to very low levels by day 7. The number of granulocytes began to increase on day 23, reaching 0.5×10^9 /L on day 37 and 1.0×10^9 /L on day 60.

The number of platelets also fell rapidly, decreasing to less than 20×10^9 /L on day 11. Platelet transfusions were administered frequently thereafter until day 65, when they were discontinued except as prophylaxis for the lung biopsy. Although the number of platelets remained below 20×10^9 /L until day 113, there was no evidence of bleeding.

Reticulocytes were first detected on day 34, reached 5 to 14×10^9 on days 40 to 67, were undetectable on days 68 to 80, and increased to 3 to 10×10^9 on day 81 until death. Hemoglobin levels are not indicated on Fig 1 since RBC transfusions were administered to maintain the level at 13.0 g/dL or higher.

Repeated analysis of blood lymphocytes showed considerable interobserver variability. The major disparity was in scoring lymphocytes, monocytes, and "monocytoid cells." In most instances, levels of blood cell were too low for automated analysis. Because of this, the levels of lymphocytes and monocytes are not presented in Fig 1.

Twelve bone marrow biopsies performed between days 1 and 16 showed complete aplasia. A biopsy on day 23 showed early recovery of granulopoiesis and erythropoiesis. A biopsy on day 62 showed increases in both lineages and small numbers of immature megakaryocytes. Samples obtained at autopsy showed about 30% cellularity, with abundant granulopoiesis and erythropoiesis but few megakaryocytes.

Pathology. Biopsy and autopsy specimens were reviewed by pathologists in Russia and the United States who were not informed of the details of the case other than that the victim had been exposed to radiation (type and circumstances unspecified).

Lung specimens showed focal and diffuse areas of fibrosis with markedly thickened alveolar septae, a mild lymphocyte infiltrate, and increased intraalveolar macrophages. There were no infiltrating granulocytes. Mild fibrinoid necrosis was detected in some blood vessels. One small focus of *Aspergillus sp* infection was detected in the left lung and a small focus of *Staphylococcus epidermidis* infection was seen in the right lung. Some areas showed hyaline membranes. These findings were interpreted as radiation pneumonitis with superimposed infection. The hyaline membranes were thought to be the result of peritermal ventilatory support with high concentration oxygen. Extensive studies for viral infection (especially cytomegalovirus [CMV]), including light and electron microscopy, immunofluorescence, and cultures, were negative.

A detailed analysis of other tissues will be published.

DISCUSSION

These data indicate that partial hematologic recovery is possible after exposure to acute total body radiation at a

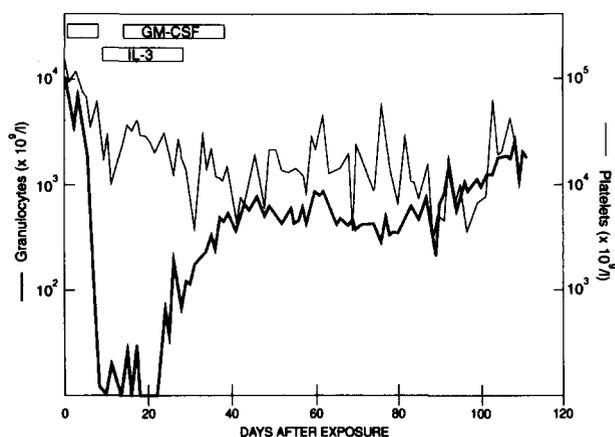


Fig 1. Hematologic course after radiation exposure. Bars indicate treatment with GM-CSF and IL-3 at doses of 250 µg/m²/d.

dose of approximately 10 Gy or more and at a very high dose rate without a transplant. The data also suggest that the dose-limiting toxicity of acute high-dose total body radiation may not be irreversible hematologic failure, as previously thought.

One concern in the interpretation of data from this case is the accuracy of measurements of radiation dose and uniformity of distribution. It is impossible to know the precise dose received by a radiation accident victim. Consequently, we used several complementary approaches, including physical measurements, computer simulation, and biologic dosimetry, to estimate dose. There was reasonably good agreement between these approaches: in no instance did we determine or estimate a dose of less than 9 Gy to any part of the body. Considerable data suggest that the midline dose may have been substantially higher, perhaps exceeding 12 Gy. We also found no evidence of shielding of any bone marrow containing area. This is consistent with the physical characteristics of the accident, including the wide field of the source and movement of the subject within the field.

Most data suggest that the subject had radiation-induced lung damage. This is not surprising in view of the high dose and dose rate of exposure. The role of bacterial, fungal, or viral infections in this case is controversial. Although radiologic abnormalities were compatible with infection, this was not documented by bronchoscopy or biopsy. Only one small focus each of *Aspergillus sp* and *Staphylococcus epidermitis* were detected at autopsy. These could not have accounted for the diffuse radiographic changes or pulmonary failure associated with the subject's death. Also, doses of amphotericin-B were insufficient to eradicate aspergillus in autopsy specimens if this had caused the earlier lung lesions. A widespread but undetected bacterial infection as the cause of the lung lesions and respiratory failure seems even less likely. There was no evidence of viral infection.

Radiation-induced lung damage is typically regarded as a slowly progressive process, occurring months to years after radiation exposure. However, this interval is more typical of radiation pneumonitis developing after fractionated radiation therapy administered at dose rates generally less than 0.1 Gy/min. In contrast, our subject received an estimated lung dose of 12 to 18 Gy at a dose rate in 1 to 2 minutes. Considerable data in animals indicate that acute whole body radiation administered under similar circumstances results in acute lung damage.¹⁻³ This more rapid course is also consistent with data from humans receiving acute high-dose total body radiation, some of whom develop "idiopathic" (non-virus-related) interstitial pneumonia within 2 months of radiation exposure.

One puzzling aspect of this case is the focal nature of the fibrosis detected on X-ray and at autopsy. We have no satisfactory explanation for this. However, focal radiation damage is reported in some animal models of acute uniform high-dose total body radiation exposure. There are also unpublished reports of similar findings in occasional radiation accident victims.

The best therapy for persons accidentally exposed to acute doses of total body radiation exceeding approximately 10 Gy is unknown. We used several treatment modalities in

this subject. The precise contribution of each, if any, to the victim's recovery is unknown because there were no untreated controls. Most radiation victims receive supportive measures, including protected environments, prophylactic antibiotics, and transfusions.¹⁵ Although several of these modalities were shown to be effective in other settings of bone marrow failure, there are no randomized trials of their efficacy in radiation accidents. Nevertheless, their favorable risk:benefit ratio makes them attractive.

It can be argued that use of hematopoietic growth factors must have played a role in the victim's recovery because considerable data in animal models indicate that recovery is impossible after doses of more than 10 Gy. However, there are problems with this interpretation. First, these models typically use much lower dose rates. Although higher dose rates are postulated to cause even greater bone marrow damage, this is unproven. Second, animals rarely if ever receive supportive measures of comparable intensity to humans. Finally, we reported data indicating partial hematopoietic recovery in 3 victims of the Chernobyl accident not receiving transplants or hematopoietic growth factors.⁸ These considerations, and the lack of controls, preclude knowing whether treatment with hematopoietic growth factors increased the likelihood or rate of hematopoietic recovery in our subject. Nevertheless, their use in radiation accident victims also seems to have a favorable risk:benefit ratio.

Considerable data suggest that gastrointestinal damage should be extremely severe or even irreversible at this dose and dose rate of acute total body radiation.¹⁻³ Although the victim had bloody diarrhea, it was of only moderate severity and resolved. This is similar to what we reported in persons exposed to high-dose radiation at the Chernobyl accident.⁸ Furthermore, persons receiving 10 Gy or more acute total body radiation as pretransplant conditioning (albeit at a considerably lower dose rate) have only moderate gastrointestinal toxicity. These data suggest that estimates of gastrointestinal toxicity of acute total body radiation based on animal models may not readily apply to humans, perhaps because it is never possible to achieve comparable levels of supportive care in animals. Whether use of hematopoietic growth factors in our subject favorably affected recovery from gastrointestinal toxicity is unknown.

Our observation of at least partial bone marrow recovery after about 10 Gy or more of acute total body radiation raises the question of whether persons with cancer can receive more acute total body radiation than they currently receive without needing a transplant. In considering this issue it is important to recall that our subject presumably had a normal bone marrow immediately before radiation exposure. Consequently, his ability to recover might have been better than that of persons with bone marrow infiltration with cancer cells or those previously treated with drugs or radiations that damage hematopoietic stem cells. Finally, data from this accident may revise estimates of mortality after future radiation accidents and potential use of nuclear weapons.

ACKNOWLEDGMENT

The Radiation Emergency Team (Chief, Prof Angelina Guskova) of the Institute of Biophysics (Chief, Prof Leonid Ilyin) was respon-

sible for analysis and management of this case. Drs Famarez Naeim (UCLA) and Vladimir Zokovsky (Institute of Biophysics) reviewed the pathologic specimens. Dr Angelica Stern of Sandoz Pharmaceuticals (Basel) supplied the GM-CSF and IL-3. Drugs were donated by Baxter Healthcare-Hyland Division (Barbara Chang), Merck-Sharp-Dome (Michelle Root), and Pfizer-Roerig (Linda Clark-Fong). Drs Henri Jammet (WHO Radiation Pathology Center, Paris, France), Theodor Fliedner (Ulm University), and Elaine Gluckman (Hospital St Louis, Paris, France) and their colleagues provided helpful comments. Drs Anika Brandt and Jon van Rood (University of Leiden) helped with HLA-typing. Dr Gary Pass (Dalhousie University) performed paramagnetic resonance analysis of dental samples. Drs H. Rodney Withers and William McBride (UCLA) provided helpful comments regarding radiation-related lung damage. Dr James Collins (UCLA) kindly reviewed the X-rays.

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