Hematopoietic Recovery After 10-Gy Acute Total Body Radiation

By Alexander E. Baranov, Giorgi D. Selidovkin, Anna Butturini, and Robert Peter Gale

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 detectable throughout the postexposure period, exceeding 0.5 x 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 radiation. 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 Nieszhev, Belarus entered the sterilization area when the 60Co source (specific activity, 8 x 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.

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 x 10^9/L (11.9 granulocytes; 0.91 lymphocytes) and the platelet count was 180 x 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 were determined by physical measurements, computer simulation, and biologic dosimetry.

Paramagnetic resonance (PMR) analysis of samples of dermal 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. The dose estimate based on bone 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. These data are summarized in Table 1.

Hospital course and treatment. Admission physical exam was unremarkable save for mild diffuse hypoplasia and parotid tenderness. The WBC was 12.6 x 10^9/L (11.9 granulocytes and 0.3 lymphocytes) and the platelet count was 225 x 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 platelet count greater than 20 x 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, we decided to use molecularly cloned hematopoietic growth factors to...
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 cefaparzone. Low-dose amphotericin-B was started shortly thereafter because of persistent fever. On day 38, an X-ray showed focal lesions in both lungs. Bronchoscopy with alveolar lavage and transbronchial biopsies were thought to be the result of peritermal radiation effects 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 perithermal 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

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.

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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 × 10⁹/L on day 37 and 1.0 × 10⁹/L on day 60.

The number of platelets also fell rapidly, decreasing to less than 20 × 10⁹/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 × 10⁹/L until day 113, there was no evidence of bleeding.

Reticulocytes were first detected on day 34, reached 5 to 14 × 10⁹/L on days 40 to 67, were undetectable on days 68 to 80, and increased to 3 to 10 × 10⁹/L 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.

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DISCUSSION

These data indicate that partial hematologic recovery is possible after exposure to acute total body radiation at a
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 the acute whole body radiation administered at dose rates generally less than 0.1 Gy/min. In contrast, our subject received an estimated dose rate of 10 Gy per minute. 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.

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