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 detectable 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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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 cefaperazone. Low-dose amphotericin-B was started shortly thereafter because of fungal infection was detected in the left lung and a small focus of *Aspergillus sp* infection was detected 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 peribronchial 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 lymphocytic infiltrate, and increased intraalveolar macrophages. There were no infiltrating granulocytes. Mild fibrinous 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 peribronchial ventilatory support with high concentration oxygen. Extensive studies for viral infection (especially cytomegalovirus [CMV]), including light and electron microscopy, immunofluorescence, and cultures, were negative.
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.13 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.

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