COMMENTARY

Is Disseminated Intravascular Coagulation the Major Cause of Mortality from Radiation at Relatively Low Whole Body Doses?

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The mechanism by which radiation exposure leads to death in mammalian organisms remains unknown, although numerous hypotheses have been discussed. At the lowest total body radiation doses leading to mammalian mortality, death occurs from the hematopoietic syndrome (HS). HS is thought to result from the cell killing effects of radiation in the bone marrow that lead to low numbers of circulating blood cells and the resultant HS symptoms, such as infection [from the loss of white blood cells (WBC)] and bleeding (presumably from the loss of platelets). Over approximately the last half century, the dose of ionizing radiation that kills half of an experimental group/exposed population, known as the LD₅₀, has been used as a parameter to compare the radiation sensitivity of various mammalian species. It is well known that the LD₅₀ is highly variable for different mammalian species; however, the bone marrow cells of different species, strains and individuals are known to have remarkably similar sensitivities to the cell killing effects of ionizing radiation (1, 2). These results suggest that the lethal effects of radiation in blood cells may not be the primary mechanism by which the HS causes death. Our results have suggested that radiation induced activation of the coagulation cascade, resulting in a condition known as disseminated intravascular coagulation (DIC), could be the major mechanism by which relatively low doses of radiation could lead to animal, including human, mortality.

Our experimental work has focused on the biological effect of solar particle event (SPE) radiation in ferrets. Ferrets exposed to SPE radiation have increased clotting times and factor deficiencies, indicating hypocoagulability (3). Our current studies in ferrets have shown that SPE proton radiation exposure at 1 Gy leads to increased bleeding times, concentrations of soluble fibrin in blood, and fibrin clotting in the livers, lungs and kidneys of irradiated ferrets within 24 h postirradiation (3, 4). The measurement of soluble fibrin in the blood is a marker for DIC in the clinic (5). DIC occurs when the clotting cascade is activated and is characterized by simultaneous bleeding and clotting. Disseminated intravascular coagulation is a serious, life-threatening condition that can occur as a result of trauma, infection or cancer (6). Ferrets exposed to 2 Gy of SPE irradiation exhibit extensive hemorrhaging through organs and other signs of DIC at 13 days postirradiation (unpublished data, Krigsfeld GS, Savage AR, Lin L and Kennedy AR).

There are relatively few cases of humans (particularly in the last half century) exposed to doses near the LD₅₀ who have not received treatments for the prevention of radiation-induced death. As the commonly used treatments for potentially lethal radiation injury have beneficial effects, human LD₅₀ values are imprecise, with estimates ranging from 3–4 Gy for young adults without medical intervention. However, human LD₅₀ values for the very young or the old may be lower (7), (between 2–3 Gy) with estimates as low as 2.43 Gy [reviewed by Lushbaugh (8)].

Remarkably different LD₅₀ values have been reported for different species. Examples of LD₅₀ values for different species (2, 9), and a range of reported human LD₅₀ values (7), are shown in Table I. The LD₅₀ values listed in Table I for the animal species indicating several strains are the average value for the different strains evaluated in the studies reviewed by Morris and Jones (2). Ferrets are the most sensitive mammalian species (9), closely followed by dogs and pigs. Pigs have a similar LD₅₀ to that of ferrets, and like the ferrets, exhibit hemorrhaging at death (2, 3) (10). The LD₅₀ in Gottingen pigs is 1.8 Gy and widespread.

References:

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