Chapter 2
Effects of Non-uniform Acute Irradiation on the Blood-Forming System

2.1 Introduction

No doubt, the patterns of organism's responses to non-uniform and uniform acute irradiation are rather different [1]. The study and prediction of such differences, as well as the revealing of their dependence on the exposure conditions (e.g., the degree of non-uniformity of irradiation and the respective whole-body dose), still remain the challenging problems. The solution of the latter requires the analysis of relevant experimental and clinical data, as well as the creation of effective research tools of studies and predictions of the effects of such exposures on the organism's vital systems, which can lead to the malfunction and illness of the latter. Such tools can be, in particular, the biologically motivated mathematical models, which are capable of predicting the dynamics of these systems after non-uniform acute irradiation.

The primary objectives of our work [2] were the development and thorough investigation of mathematical models, which describe the dynamics of the major hematopoietic lineages (the thrombopoietic, erythropoietic, granulopoietic, and lymphopoietic systems) under non-uniform acute irradiation. These models are based on the developed mathematical models of the dynamics of these systems in mammals (rodents) exposed to uniform acute irradiation (see Chap. 1, as well as [3–8]). The description of the mathematical models of the dynamics of the major hematopoietic lineages in mammals (rodents) exposed to non-uniform and uniform acute irradiation, the comparative analysis of the results obtained in their framework, revealing the causes, which can lead to differences in the responses of these systems to uniform and non-uniform acute irradiation, as well as the discussion of possible ways of extension of these models to the study of the effects of non-uniform acute irradiation on the major hematopoietic lineages in humans are given below.

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2.2 Mathematical Models

The models of the dynamics of the thrombopoietic, erythropoietic, granulopoietic, and lymphopoietic systems in mammals (rodents) after non-uniform acute irradiation are based on the developed models of the dynamics of these major hematopoietic lineages after uniform acute irradiation (see Chap. 1, as well as [3–8]).

Summarizing all the stated in Chap. 1, the mathematical models of the dynamics of the major hematopoietic lineages in mammals (rodents) after uniform acute irradiation can be presented in the following way. Specifically, these models consider the basic cell compartments according to the degree of maturity and differentiation of cells of the respective hematopoietic lineages:

- X_1, the precursor cells capable of dividing (from stem cells in the microenvironment, which predetermine their differentiation toward the aforementioned hematopoietic lineages, to morphologically identifiable dividing maturing bone marrow cells in these hematopoietic lineages, namely to megakaryocytoblasts in the thrombopoietic system, to polychromatophilic erythroblasts in the erythropoietic system, to myelocytes in the granulopoietic system, and to lymphoblasts in the lymphopoietic system);
- X_2, the precursor cells incapable of dividing (nondividing maturing bone marrow cells in the hematopoietic lineages on hand, namely from promegakaryocytes to mature megakaryocytes in the thrombopoietic system, from orthochromatic erythroblasts to reticulocytes in the erythropoietic system, from metamyelocytes to granulocytes in the granulopoietic system, and lymphoid cells in the lymphopoietic system);
- X_3, the mature cells (the functional blood cells of the hematopoietic lineages on hand, namely thrombocytes (blood platelets) in the thrombopoietic system, blood erythrocytes in the erythropoietic system, blood granulocytes in the granulopoietic system, and blood lymphocytes in the lymphopoietic system);
- X_4, the tissue granulocytes (appears only in the granulopoiesis model).

The cells of a radiosensitive compartment X_i ($i = 1, \ldots, n$) are split into three groups, according to their response to irradiation:

- X_i^{ud}, undamaged cells;
- X_i^{d}, damaged cells that die within 1 or 2 days (mitotic death);
- X_i^{hd}, heavily damaged cells that die within several hours (interphase death).

In turn, the cells of a radioresistant compartment X_i ($i = n+1, \ldots, m$) are considered as undamaged cells X_i^{ud} ($i = n + 1, \ldots, m$). Here m is the total number of cell compartments considered in the model of the respective hematopoietic lineage and n is the number of radiosensitive cell compartments among them. In particular, only X_1 cells are radiosensitive in the thrombopoietic system (i.e., $n = 1$, $m = 3$). In the erythropoietic system, X_1 and X_2 cells are radiosensitive (i.e., $n = 2$, $m = 3$). In the granulopoietic system, X_1, X_2, X_3, and X_4 cells are radiosensitive, though in

a different degree (i.e., $n = m = 4$). In the lymphopoietic system, X_1, X_2, and X_3 cells are radiosensitive (i.e., $n = m = 3$).

The variables of the models are the concentrations of radiosensitive X_i^{ud}, X_i^{d}, X_i^{hd} $(i = 1, \ldots, n)$ cells and the concentrations of radioresistant X_i^{ud} $(i = n+1, \ldots, m)$ cells: x_i^{ud}, x_i^{d}, x_i^{hd} $(i = 1, \ldots, n)$ and x_i^{ud} $(i = n+1, \ldots, m)$, respectively. By cell concentration, we mean the ratio of the total number of cells of a certain group to the total blood volume. The dynamics of the concentrations of X_i^{ud} $(i = 1, \ldots, n)$, X_i^{d} $(i = 1, \ldots, n)$, X_i^{hd} $(i = 1, \ldots, n)$, and X_i^{ud} $(i = n+1, \ldots, m)$ cells in the respective major hematopoietic lineages after uniform acute irradiation is described by the following differential equations (see Chap. 1 and the references therein for the details):

$$\frac{dx_1^{\mathrm{ud}}}{dt} = Bx_1^{\mathrm{ud}} - \gamma x_1^{\mathrm{ud}}, \tag{2.1}$$

$$\frac{dx_2^{\mathrm{ud}}}{dt} = \gamma x_1^{\mathrm{ud}} - Fx_2^{\mathrm{ud}}, \tag{2.2}$$

$$\frac{dx_3^{\mathrm{ud}}}{dt} = Fx_2^{\mathrm{ud}} - \psi x_3^{\mathrm{ud}}, \tag{2.3}$$

$$\frac{dx_4^{\mathrm{ud}}}{dt} = \psi x_3^{\mathrm{ud}} - \xi x_4^{\mathrm{ud}}, \tag{2.4}$$

$$\frac{dx_i^{\mathrm{d}}}{dt} = -\mu x_i^{\mathrm{d}} \quad (i = 1, \ldots, n), \tag{2.5}$$

$$\frac{dx_i^{\mathrm{hd}}}{dt} = -\nu x_i^{\mathrm{hd}} \quad (i = 1, \ldots, n). \tag{2.6}$$

In Eqs. (2.1)–(2.3), the parameter B is the specific reproduction rate of X_1^{ud} cells, the coefficients γ and F are the specific rates of transfer of cells from group X_1^{ud} to group X_2^{ud} and from group X_2^{ud} to group X_3^{ud}, respectively. In the thrombopoiesis, erythropoiesis, and lymphopoiesis models, the coefficient ψ in Eq. (2.3) denotes the specific rate of the natural death of X_3^{ud} cells. In the granulopoiesis model, the coefficient ψ in Eqs. (2.3) and (2.4) stands for the specific rate of transfer of cells from group X_3^{ud} to group X_4^{ud} (from blood to tissues) and the coefficient ξ in Eq. (2.4) is the specific rate of the natural death of X_4^{ud} cells. In Eqs. (2.5) and (2.6), the coefficients μ and ν are the specific death rates of damaged and heavily damaged cells, respectively.

The formula describing the parameter B in Eq. (2.1) takes into account the negative-feedback control of the specific reproduction rate of X_1^{ud} cells in the major hematopoietic lineages (see Chap. 1 and the references therein for the details):

$$B = \frac{\alpha}{1 + \beta\Big[\sum\limits_{i=1}^{n} \theta_i \left(x_i^{\mathrm{ud}} + \phi x_i^{\mathrm{d}} + \varphi x_i^{\mathrm{hd}}\right) + \sum\limits_{i=n+1}^{m} \theta_i x_i^{\mathrm{ud}}\Big]}. \tag{2.7}$$

Here $\theta_1 = 1$ by definition, the parameters θ_i ($i = 2, \ldots, m$), β, ϕ, and φ are constants.

The model of the granulopoietic system considers the regulatory mechanism of the specific rate of the granulocyte supply from the bone marrow to the blood flow by the introduction of the variable parameter F. The latter accounts for the contributions of the undamaged, damaged, and heavily damaged blood granulocytes (X_3^{ud}, X_3^{d}, and X_3^{hd} cells) to this regulatory mechanism (see Chap. 1 and the references therein for the details):

$$F = \delta \frac{1 + [m/(\bar{x}_3)^2]\left(x_3^{\mathrm{ud}} + x_3^{\mathrm{d}} + x_3^{\mathrm{hd}}\right)^2}{1 + [l/(\bar{x}_3)^2]\left(x_3^{\mathrm{ud}} + x_3^{\mathrm{d}} + x_3^{\mathrm{hd}}\right)^2}, \tag{2.8}$$

where constants δ and $\delta m/l$ are the maximal and minimal values of the specific rate of granulocyte supply from the bone marrow to the blood flow. Note that the parameter F is constants ($F \equiv \delta$) in the models of the thrombopoietic, erythropoietic, and lymphopoietic systems.

In turn, the model of the thrombopoietic system takes into account the regulatory mechanism of megakaryocyte ploidy by the introduction of the ploidy coefficient f. The latter is described by the decreasing function of the thrombocyte concentration x_3^{ud} (see Chap. 1 and the references therein for the details):

$$f = \frac{1}{\lambda + (1 - \lambda)(x_3^{\mathrm{ud}}/\bar{x}_3)}. \tag{2.9}$$

Here λ is a dimensionless constant and $\bar{x}_3$ is the normal concentration of thrombocytes (X_3 cells). In the thrombopoiesis model, the first term on the right-hand side of Eq. (2.2) is multiplied by the factor f and the first term on the right-hand side of Eq. (2.3) is multiplied by the factor σ, the latter being the average number of thrombocytes produced by one megakaryocyte.

The initial conditions for Eqs. (2.1)–(2.6) read (see Chap. 1 and the references therein for the details):

$$x_i^{\mathrm{ud}}(0) = \bar{x}_i \exp(-D/D_i^0) \quad (i = 1, \ldots, n), \tag{2.10}$$

$$x_i^{\mathrm{d}}(0) = \bar{x}_i \frac{1}{1 + \rho_i}[1 - \exp(-D/D_i^0)] \quad (i = 1, \ldots, n), \tag{2.11}$$

$$x_i^{\mathrm{hd}}(0) = \bar{x}_i \frac{\rho_i}{1 + \rho_i}[1 - \exp(-D/D_i^0)] \quad (i = 1, \ldots, n), \tag{2.12}$$

$$x_i^{\mathrm{ud}}(0) = \bar{x}_i \quad (i = n + 1, \ldots, m), \tag{2.13}$$

where

$$\rho_i = \frac{1 - \exp(-D/D_i^{00})}{\exp(-D/D_i^{00}) - \exp(-D/D_i^0)} \quad (i = 1, \ldots, n). \tag{2.14}$$

Here $\bar{x}_i$ $(i = 1, \ldots, m)$ is the normal concentration of X_i $(i = 1, \ldots, m)$ cells. The parameter D is a dose of acute irradiation. The coefficient D_i^0 $(i = 1, \ldots, n)$ is equivalent to the conventional dose D_0, after exposure to which the number of X_i cells left undamaged is $e = 2.718\ldots$ times smaller than their initial number [9]. The coefficient D_i^{00} $(i = 1, \ldots, n)$ is the dose, after exposure to which the number of X_i^{ud} $(i = 1, \ldots, n)$ cells, which do not undergo the interphase death, is $e = 2.718\ldots$ times smaller than their initial number.

It is important to emphasize that the developed models, which describe the dynamics of the major hematopoietic lineages after uniform acute irradiation, explicitly embody the main characteristic of irradiation, namely the dose D of such exposure, as well as the radiobiological parameters D_i^0 and D_i^{00} $(i = 1, \ldots, n)$, which characterize the radiosensitivity of the respective cells of these systems.

To extend the models of the dynamics of the major hematopoietic lineages (the thrombopoietic, erythropoietic, granulopoietic, and lymphopoietic systems) in mammals (rodents) after uniform acute irradiation with the aim of the describing, in their framework, of the dynamics of these system after non-uniform acute irradiation, the following approach is used. It is assumed that non-uniform acute irradiation of the hematopoietic tissue, which contains the radiosensitive cells of the systems on hand, can be considered as a composition of k uniform acute exposures of its k parts with dose rates N_j $(j = 1, \ldots, k)$ and a duration τ, respectively. The ratio of the mass of j-th part of the hematopoietic tissue to the total mass of the latter (i.e., the fraction of mass of j-th part of the hematopoietic tissue) before the onset of non-uniform acute irradiation is denoted by Ω_j $(j = 1, \ldots, k)$. In accordance with these assumptions, the extended models, which describe the dynamics of the major hematopoietic lineages after non-uniform acute irradiation, consider undamaged, damaged, and heavily damaged radiosensitive cells [X_{ij}^{ud}, X_{ij}^{d}, X_{ij}^{hd} $(i = 1, \ldots, n; j = 1, \ldots, k)$ cells] and radioresistant cells [X_{ij}^{ud} $(i = n + 1, \ldots, m; j = 1, \ldots, k)$ cells] belonging to the j-th $(j = 1, \ldots, k)$ part of the hematopoietic tissue. Here the index i specifies a certain cell compartment and the index j specifies a certain part of the hematopoietic tissue. The variables of these models are the concentrations of cells of the aforementioned groups: x_{ij}^{ud}, x_{ij}^{d}, x_{ij}^{hd} $(i = 1, \ldots, n; j = 1, \ldots, k)$ and x_{ij}^{ud} $(i = n+1, \ldots, m; j = 1, \ldots, k)$. It is obvious that the concentrations x_i^{ud}, x_i^{d}, x_i^{hd} $(i = 1, \ldots, n)$ and x_i^{ud} $(i = n + 1, \ldots, m)$ can be expressed in terms of the concentrations x_{ij}^{ud}, x_{ij}^{d}, x_{ij}^{hd} $(i = 1, \ldots, n; j = 1, \ldots, k)$ and x_{ij}^{ud} $(i = n + 1, \ldots, m; j = 1, \ldots, k)$ in the following way:

$$x_i^{\mathrm{ud}} = \sum_{j=1}^{k} x_{ij}^{\mathrm{ud}} \quad (i = 1, \ldots, n), \tag{2.15}$$

$$x_i^{\mathrm{d}} = \sum_{j=1}^{k} x_{ij}^{\mathrm{d}} \quad (i = 1, \ldots, n), \tag{2.16}$$

$$x_i^{\mathrm{hd}} = \sum_{j=1}^{k} x_{ij}^{\mathrm{hd}} \quad (i = 1, \ldots, n), \tag{2.17}$$

$$x_i^{\mathrm{ud}} = \sum_{j=1}^{k} x_{ij}^{\mathrm{ud}} \quad (i = n+1, \ldots, m). \tag{2.18}$$

Taking into account the one-target–one-hit theory of cell damage [10], according to which the damage rate of radiosensitive cells is proportional to the dose rate of irradiation, and taking into consideration the extremely short duration τ of non-uniform acute irradiation, the dynamics of the concentrations of undamaged, damaged, and heavily damaged radiosensitive X_{ij}^{ud}, X_{ij}^{d}, X_{ij}^{hd} $(i = 1, \ldots, n; j = 1, \ldots, k)$ cells during the exposure can be described by the system of "fast" equations, whereas the concentrations of radioresistant X_{ij}^{ud} $(i = n+1, \ldots, m; j = 1, \ldots, k)$ cells can be considered constant ones:

$$\frac{dx_{ij}^{\mathrm{ud}}}{dt} = -\frac{N_j}{D_i^0} x_{ij}^{\mathrm{ud}} \quad (i = 1, \ldots, n; j = 1, \ldots, k), \tag{2.19}$$

$$\frac{dx_{ij}^{\mathrm{d}}}{dt} = \frac{N_j}{D_i^0} \frac{1}{1+\rho_{ij}} x_{ij}^{\mathrm{ud}} \quad (i = 1, \ldots, n; j = 1, \ldots, k), \tag{2.20}$$

$$\frac{dx_{ij}^{\mathrm{hd}}}{dt} = \frac{N_j}{D_i^0} \frac{\rho_{ij}}{1+\rho_{ij}} x_{ij}^{\mathrm{ud}} \quad (i = 1, \ldots, n; j = 1, \ldots, k), \tag{2.21}$$

$$\frac{dx_{ij}^{\mathrm{ud}}}{dt} = 0 \quad (i = n+1, \ldots, m; j = 1, \ldots, k), \tag{2.22}$$

where N_j $(j = 1, \ldots, k)$ is the dose rate of the uniform acute exposure of j $(j = 1, \ldots, k)$ part of the hematopoietic tissue; the parameter D_i^0 $(i = 1, \ldots, n)$ is equivalent to the conventional dose D_0, after exposure to which the number of X_i cells left undamaged is exp(-1) (i.e., 36.79 %) of their initial number [9]. The ratio N_j/D_i^0 on the right-hand side of Eq. (2.19), which describes the dynamics of concentration of radiosensitive cells X_{ij}^{ud}, is the specific rate of decrease of the concentration of these cells due to their radiation-induced damage. One part of them transfers into the group of damaged cells X_{ij}^{d} [Eq. (2.20)] and the other part passes to the group of heavily damaged cells X_{ij}^{hd} [Eq. (2.21)]. The ratio of these parts is denoted by ρ_{ij}.

The initial conditions for Eqs. (2.19)–(2.22) are concentrations of X_{ij}^{ud} $(i = 1, \ldots, n; j = 1, \ldots, k)$ cells, X_{ij}^{d} $(i = 1, \ldots, n; j = 1, \ldots, k)$ cells, X_{ij}^{hd} $(i = 1, \ldots, n; j = 1, \ldots, k)$ cells, and X_{ij}^{ud} $(i = n+1, \ldots, m; j = 1, \ldots, k)$ cells before the onset of non-uniform acute irradiation. In particular, in the case of irradiation of a healthy individual that has not previously been exposed to radiation, the concentrations of damaged X_{ij}^{d} $(i = 1, \ldots, n; j = 1, \ldots, k)$ cells and heavily

damaged X_{ij}^{hd} $(i = 1,\ldots,n; j = 1,\ldots,k)$ cells are equal to zero, whereas the concentrations of radiosensitive X_{ij}^{ud} $(i = 1,\ldots,n; j = 1,\ldots,k)$ cells and radioresistant X_{ij}^{ud} $(i = n+1,\ldots,m; j = 1,\ldots,k)$ cells are equal to their normal values. As a result, the initial conditions for Eqs. (2.19)–(2.22) take the following form:

$$x_{ij}^{\mathrm{ud}}(0) = \bar{x}_i \Omega_j \quad (i = 1,\ldots,n; j = 1,\ldots,k), \tag{2.23}$$

$$x_{ij}^{\mathrm{d}}(0) = 0 \quad (i = 1,\ldots,n), \tag{2.24}$$

$$x_{ij}^{\mathrm{hd}}(0) = 0 \quad (i = 1,\ldots,n), \tag{2.25}$$

$$x_{ij}^{\mathrm{ud}}(0) = \bar{x}_i \Omega_j \quad (i = n+1,\ldots,m; j = 1,\ldots,k). \tag{2.26}$$

For the considered case of the constant dose rate N_j, which the j-th part of the hematopoietic tissue is exposed to, Eqs. (2.19)–(2.22) with the initial conditions (2.23)–(2.26) can be integrated explicitly. The obtained expressions for the concentrations of X_{ij}^{ud}, X_{ij}^{d}, X_{ij}^{hd} $(i = 1,\ldots,n; j = 1,\ldots,k)$ cells and X_{ij}^{ud} $(i = n+1,\ldots,m; j = 1,\ldots,k)$ cells can be used as the initial conditions for the concentrations of these cells:

$$x_{ij}^{\mathrm{ud}}(0) = \bar{x}_i\, \Omega_j \exp(-D_j/D_i^0) \quad (i = 1,\ldots,n; j = 1,\ldots,k), \tag{2.27}$$

$$x_{ij}^{\mathrm{d}}(0) = \bar{x}_i\, \Omega_j \frac{1}{1+\rho_{ij}}[1 - \exp(-D_j/D_i^0)] \quad (i = 1,\ldots,n; j = 1,\ldots,k), \tag{2.28}$$

$$x_{ij}^{\mathrm{hd}}(0) = \bar{x}_i\, \Omega_j \frac{\rho_{ij}}{1+\rho_{ij}}[1 - \exp(-D_j/D_i^0)] \quad (i = 1,\ldots,n; j = 1,\ldots,k), \tag{2.29}$$

$$x_{ij}^{\mathrm{ud}}(0) = \bar{x}_i\, \Omega_j \quad (i = n+1,\ldots,m; j = 1,\ldots,k), \tag{2.30}$$

where

$$\rho_{ij} = \frac{1 - \exp(-D_j/D_i^{00})}{\exp(-D_j/D_i^{00}) - \exp(-D_j/D_i^0)} \quad (i = 1,\ldots,n; j = 1,\ldots,k). \tag{2.31}$$

Here D_j is the dose of irradiation of j-th part of the hematopoietic tissue. The parameter D_i^0 $(i = 1,\ldots,n)$, as it was specified above, is equivalent to the conventional dose D_0, after exposure to which the number of X_i^{ud} $(i = 1,\ldots,n)$ cells left undamaged is $\exp(-1)$ (i.e., 36.79 %) of their initial number [9]. The parameter D_i^{00} $(i = 1,\ldots,n)$ is the dose, after exposure to which the number of X_i^{ud} $(i = 1,\ldots,n)$ cells, which do not undergo the interphase death, is $\exp(-1)$ (i.e., 36.79 %) of their initial number.

By virtue of Eqs. (2.15)–(2.18), Eqs. (2.27)–(2.30) are reduced to the following equations:

$$x_i^{\mathrm{ud}}(0) = \bar{x}_i \sum_{j=1}^{k} \Omega_j \exp(-D_j/D_i^0) \quad (i = 1, \ldots, n), \tag{2.32}$$

$$x_i^{\mathrm{d}}(0) = \bar{x}_i \sum_{j=1}^{k} \Omega_j \frac{1}{1+\rho_{ij}}[1 - \exp(-D_j/D_i^0)] \quad (i = 1, \ldots, n), \tag{2.33}$$

$$x_i^{\mathrm{hd}}(0) = \bar{x}_i \sum_{j=1}^{k} \Omega_j \frac{\rho_{ij}}{1+\rho_{ij}}[1 - \exp(-D_j/D_i^0)] \quad (i = 1, \ldots, n), \tag{2.34}$$

$$x_i^{\mathrm{ud}}(0) = \bar{x}_i \quad (i = n+1, \ldots, m). \tag{2.35}$$

Thus, the dynamics of the major hematopoietic lineages after non-uniform acute irradiation can be described by Eqs. (2.1)–(2.6) with the initial conditions (2.32)–(2.35). It is important to emphasize that these models explicitly embody the main characteristic of such exposure, namely the doses D_j ($j = 1, \ldots, k$) of irradiation of k parts of the hematopoietic tissue, as well as the radiobiological parameters D_i^0 and D_i^{00} ($i = 1, \ldots, n$), which characterize the radiosensitivity of the respective cells of these systems.

Note that the models of the dynamics the major hematopoietic lineages after non-uniform acute irradiation [Eqs. (2.1)–(2.6) with the initial conditions (2.32)–(2.35)] are reduced to the models of the dynamics of these systems after uniform acute irradiation [Eqs. (2.1)–(2.6) with the initial conditions (2.10)–(2.13)] if the model parameters k and Ω_1 are taken to be equal to unity ($k = 1$, $\Omega_1 = 1$) and $D_1 \equiv D$.

For the numerical studies, the models of the major hematopoietic lineages in mammals (rodents) exposed to uniform and non-uniform acute irradiation are rewritten in terms of the new dimensionless variables, the latter being the ratios of the dimension concentrations of the considered cells to their normal values.

The values of the independent parameters of the models of the major hematopoietic lineages in rodents (rats, mice) are given in Tables 1.1, 1.2, 1.3, and 1.4.

2.3 Distinctive Features of Responses of Major Hematopoietic Lineages to Non-uniform and Uniform Acute Irradiation

The developed models of the thrombopoietic, erythropoietic, granulopoietic, and lymphopoietic systems are applied to study the responses of these major hematopoietic lineages in rodents (mice, rats) to non-uniform and uniform acute irradiation and to analyze the distinctions between them. In this series of the modeling simulations, the number k of parts of the hematopoietic tissue, which were exposed to different

doses D_j ($j = 1, \ldots, k$), is fixed and taken to be equal to four. The exposure doses D_j ($j = 1, \ldots, 4$) of these equal parts are chosen so that the averaged exposure dose (i.e., the whole-body dose) is equal to the dose of uniform acute irradiation D reported in [9, 11]. The variation of the degree of non-uniformity of acute irradiation is simulated by the respective variation of exposure doses D_j ($j = 1, \ldots, k$). In turn, the dose of uniform acute irradiation is taken to be equal to the whole-body dose of non-uniform exposure. The obtained modeling results are presented in Figs. 2.1, 2.2, 2.3, and 2.4.

Figure 2.1 shows the modeling dynamics of concentrations of blood thrombocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in the thrombopoietic system after uniform acute irradiation and after two non-uniform acute radiation exposures with the equal values of their whole-body doses. As one can see, the concentrations of X_3 cells and of X_1^{ud} cells decrease and approach their minimal levels, which are higher in the cases of non-uniform exposures than those in the case of uniform acute irradiation. The time intervals required to reach these minimal levels are shorter in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. Then the concentrations of these cells increase and achieve their maximal values, which are smaller in the cases of non-uniform exposures than those in the case

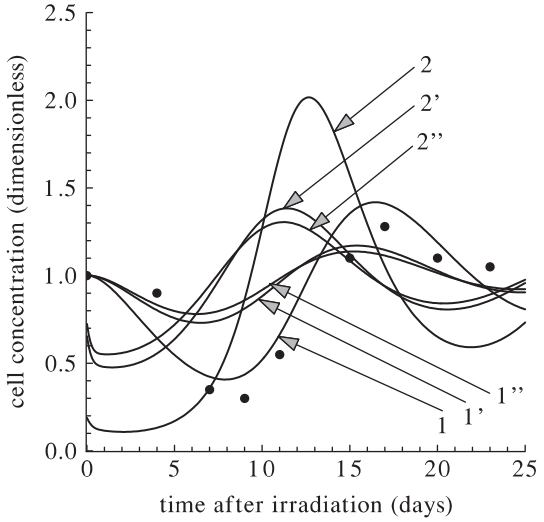

Fig. 2.1 The modeling results on the dynamics of the dimensionless concentrations of blood thrombocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in rodents (*mice*) exposed to uniform acute irradiation with the dose of 4 Gy (*curves 1 and 2*) and in mice exposed to two non-uniform acute exposures with the averaged doses of 4 Gy, at which the doses of irradiation of 4 equal parts of the hematopoietic tissue are equal to 0.25, 0.25, 0.5, 15.0 Gy (*curves 1' and 2'*) and to 0.0625, 0.0625, 0.125, 15.75 Gy (*curves 1" and 2"*). The experimental data [9] are given by mean values of concentration of blood thrombocytes in mice after uniform acute irradiation with the dose of 4 Gy (*circles*)

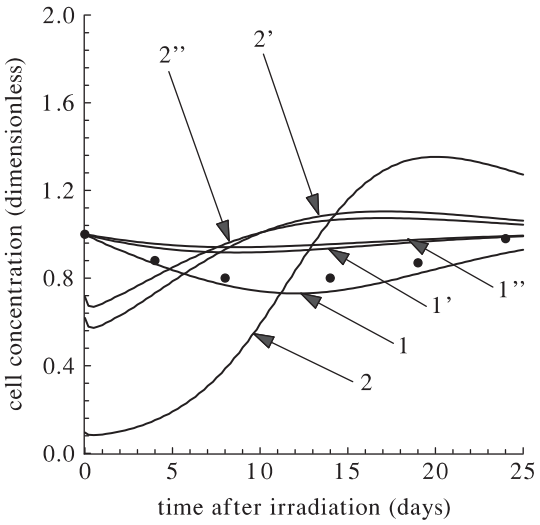

Fig. 2.2 The modeling results on the dynamics of the dimensionless concentrations of blood erythrocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in rodents (*rats*) exposed to uniform acute irradiation with the dose of 4 Gy (*curves 1 and 2*) and in rats exposed to two non-uniform acute exposures with the averaged doses of 4 Gy, at which the doses of irradiation of 4 equal parts of the hematopoietic tissue are equal to 0.25, 0.25, 0.5, 15.0 Gy (*curves 1' and 2'*) and to 0.0625, 0.0625, 0.125, 15.75 Gy (*curves 1" and 2"*). The experimental data [11] are given by mean values of concentration of blood erythrocytes in rats after uniform acute irradiation with the dose of 4 Gy (*circles*)

of uniform acute irradiation. The time intervals required to reach these maximal levels are shorter in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. Further, the concentrations of X_3 cells and of X_1^{ud} cells decrease again and, after damped oscillations, return to their normal values in shorter time intervals after non-uniform acute exposures than after uniform one, as computations show. It is important to emphasize that, as it follows from Fig. 2.1, the modeling results on the dynamics of the concentration of X_3 cells after uniform acute irradiation agree with the respective experimental data [9] on the kinetics of the concentration of thrombocytes in mice.

Figure 2.2 displays the modeling dynamics of concentrations of blood erythrocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in the erythropoietic system after uniform acute irradiation and after two non-uniform acute radiation exposures with the equal values of their whole-body doses. Figure 2.2 shows that the concentration of X_1^{ud} cells decreases and approaches its minimal level, which is higher in the case of non-uniform acute exposure than that in the case of uniform acute irradiation. The time interval required to reach this minimal level is slightly shorter in the case of non-uniform acute exposure than that in the case of uniform acute irradiation. Then the concentration of X_1^{ud} cells increases and achieves its maximal value, which is smaller in the case

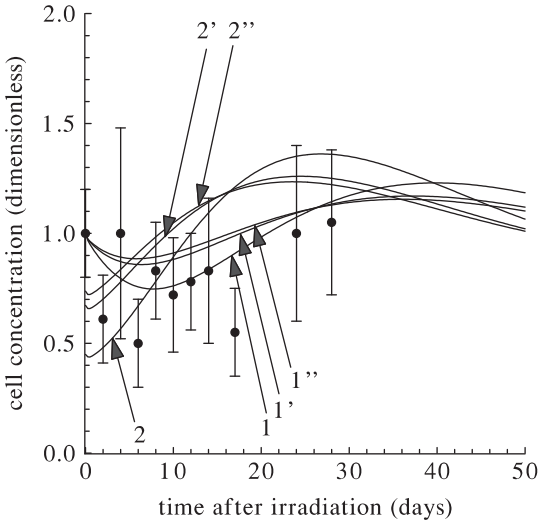

Fig. 2.3 The modeling results on the dynamics of the dimensionless concentrations of blood granulocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in rodents (*rats*) exposed to uniform acute irradiation with the dose of 2 Gy (*curves 1 and 2*) and in rats exposed to two non-uniform acute exposures with the averaged doses of 2 Gy, at which the doses of irradiation of 4 equal parts of the hematopoietic tissue are equal to 0.25, 0.25, 0.5, 7.0 Gy (*curves 1' and 2'*) and to 0.0625, 0.0625, 0.125, 7.75 Gy (*curves 1" and 2"*). The experimental data [11] are given by mean values of dimensionless concentration of blood neutrophilic granulocytes (*circles*) and by mean square deviations from these mean values in rats after uniform acute irradiation with the dose of 2 Gy

of non-uniform exposure than that in the case of uniform acute irradiation. The time interval required to reach this maximal level is shorter in the case of non-uniform acute exposure than that in the case of uniform acute irradiation. Further, the concentration of X_1^{ud} cells decreases again and, after overdamped oscillations, returns to its normal value in shorter time interval after non-uniform acute irradiation than after uniform one, as computations show. Figure 2.2 also demonstrates that the concentration of X_3 cells decreases and approaches its minimal level, which is higher in the case of non-uniform acute exposure than that in the case of uniform acute irradiation. The time interval required to reach this minimal level is slightly shorter in the case of non-uniform acute exposure than that in the case of uniform acute irradiation. Then the concentration of X_3 cells increases and returns, aperiodically, to the normal level in shorter time interval after non-uniform acute exposure than after uniform one, as computations show. It is important to outline that, as it follows from Fig. 2.2, the modeling results on the dynamics of the concentration of X_3 cells after uniform acute irradiation agree with the respective experimental data [11] on the kinetics of the concentration of erythrocytes in rats.

Figure 2.3 presents the modeling dynamics of concentrations of blood granulocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of

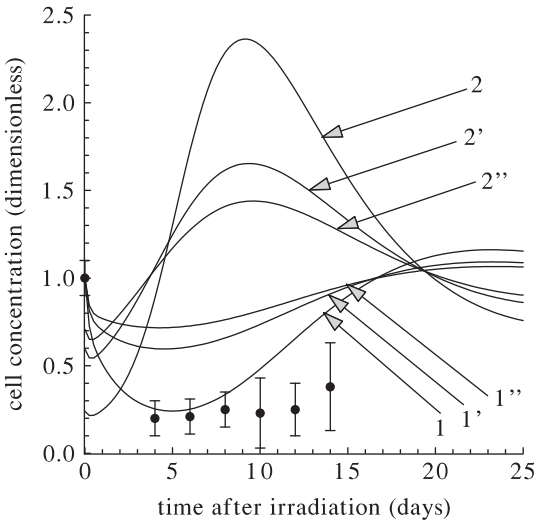

Fig. 2.4 The modeling results on the dynamics of the dimensionless concentrations of blood lymphocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in rodents (*rats*) exposed to uniform acute irradiation with the dose of 2 Gy (*curves 1 and 2*) and in rats exposed to two non-uniform acute exposures with the averaged doses of 2 Gy, at which the doses of irradiation of 4 equal parts of the hematopoietic tissue are equal to 0.25, 0.25, 0.5, 7.0 Gy (*curves 1' and 2'*) and to 0.0625, 0.0625, 0.125, 7.75 Gy (*curves 1" and 2"*). The experimental data [11] are given by mean values of dimensionless concentration of blood lymphocytes (*circles*) and by mean square deviations from these mean values in rats after uniform acute irradiation with the dose of 2 Gy

dividing (X_1^{ud} cells) in the granulopoietic system after uniform acute irradiation and after two non-uniform acute radiation exposures with the equal values of their whole-body doses. As one can see, the concentrations of X_3 cells and of X_1^{ud} cells decrease and approach their minimal levels, which are higher in the cases of non-uniform exposures than those in the case of uniform acute irradiation. The time intervals required to reach these minimal levels are slightly shorter in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. Then the concentrations of X_3 cells and of X_1^{ud} cells increase and achieve their maximal values, which are smaller in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. The time intervals required to reach these maximal levels are shorter in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. Further, the concentrations of X_3 cells and of X_1^{ud} cells decrease again and, after damped oscillations, return to their normal values in shorter time intervals after non-uniform acute exposures than after uniform one, as computations show. It is important to underscore that, as it follows from Fig. 2.3, the modeling results on the dynamics of the concentration of X_3 cells after uniform acute irradiation agree with the respective experimental data [11] on the kinetics of the concentration of granulocytes in rats.

Figure 2.4 displays the modeling dynamics of concentrations of blood lymphocytes (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in the lymphopoietic system after uniform acute irradiation and after two non-uniform acute radiation exposures with the equal values of their whole-body doses. As one can infer from this figure, the concentrations of X_3 cells and of X_1^{ud} cells decrease and approach their minimal levels, which are higher in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. The time intervals required to reach these minimal levels are slightly shorter in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. Then the concentrations of X_3 cells and of X_1^{ud} cells increase and achieve their maximal values, which are smaller in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. The time intervals required to reach these maximal levels are slightly shorter in the cases of non-uniform acute exposures than those in the case of uniform acute irradiation. Further, the concentrations of X_3 cells and of X_1^{ud} cells decrease again and, after damped oscillations, return to their normal values in shorter time intervals after non-uniform acute exposures than after uniform one, as computations show. It is important to note that, as it follows from Fig. 2.4, the modeling results on the dynamics of the concentration of X_3 cells after uniform acute irradiation agree with the respective experimental data [11] on the kinetics of the concentration of lymphocytes in rats.

The analysis of the modeling results presented in Figs. 2.1, 2.2, 2.3, and 2.4 allows one to reveal the following. The modeling dynamics of the concentrations of X_3 cells and X_1^{ud} cells in the systems on hand after non-uniform and uniform acute irradiation have the similar character. However, there are quantitative distinctions between them, these distinctions being more significant in the case of more pronounced non-uniformity of acute irradiation. Specifically, the minimal levels, up to which the concentrations of X_3 cells and X_1^{ud} cells in each considered major hematopoietic lineage decrease after non-uniform acute irradiation, are higher than those after uniform acute irradiation at equal values of whole-body doses of these exposures. The differences between these levels are more valuable in the case of more pronounced non-uniformity of acute irradiation. In turn, as computations show, the concentrations of X_3 cells and X_1^{ud} cells in the major hematopoietic lineages reach their normal levels faster after non-uniform acute irradiation than those after uniform acute exposure at equal values of whole-body doses of these exposures. The time intervals required to reach their normal levels are shorter in the case of more pronounced non-uniformity of acute irradiation. Thus, the developed models of the major hematopoietic lineages predict the smaller depletion of pools of functional blood cells and their bone marrow precursor cells capable of dividing in the major hematopoietic lineages of rodent and the faster recovering of the pools of these cells after non-uniform acute irradiation than those after uniform acute irradiation at the same whole-body doses of such exposures. These modeling findings conform with experimental observation [12].

The juxtaposition of the modeling results on the dynamics of concentrations of functional blood cells (X_3 cells) and their undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) in the major hematopoietic lineages after uniform

and non-uniform acute irradiation at the same whole-body doses of these exposures elucidates the following feature. The levels, up to which the concentrations of functional blood cells (X_3 cells) decrease, are higher and the time intervals needed for returning of these concentrations to their normal levels are shorter, if the concentrations of their bone marrow precursor cells capable of dividing, which are left undamaged after acute irradiation (X_1^{ud} cells), are higher (Figs. 2.1, 2.2, 2.3, and 2.4). In turn, the concentrations of the bone marrow precursor cells capable of dividing (X_1 cells), which are left undamaged after non-uniform acute irradiation are higher in comparison with those, which are left undamaged after uniform acute irradiation Figs. 2.1, 2.2, 2.3, and 2.4.

These modeling findings allow one to reveal the reason–consequence relationships, which are resulted in observed distinctions in the responses of the major hematopoietic lineages to non-uniform and uniform acute irradiation at the same whole-body doses of such exposures. Specifically, the less pronounced depletions of the pools of the functional blood cells (X_3 cells) and the faster recovery of these cell pools in the major hematopoietic lineages after non-uniform acute irradiation to compare with those after uniform acute irradiation (at the same whole-body doses of such exposures) are due to the higher levels of concentrations of the bone marrow precursor cells capable of dividing (X_1 cells), which are left undamaged after non-uniform acute irradiation, in comparison with those, which are left undamaged after uniform acute irradiation. Taking into account that the compartment of X_1 cells includes stem cells and their committed progenies capable of dividing, the obtained modeling results testify to the principal role of these cells in the process of damage and recovery in the major hematopoietic lineages after non-uniform and uniform acute irradiation, as well as elucidate the role of these cells in weakening the hematopoietic subsyndrome of acute radiation syndrome under non-uniform acute irradiation. Additionally, the modeling results attest to the inefficiency of the employment, for the prognostic purposes, of the whole-body dose D of non-uniform acute irradiation.

2.4 Distinctive Features of Responses of Major Hematopoietic Lineages to Partial and Uniform Acute Irradiation

The models of the major hematopoietic lineages (the thrombopoietic, erythropoietic, granulopoietic, and lymphopoietic systems) are used to compare, in detail, the responses of these systems to uniform acute irradiation and to partial acute irradiation. The latter is a particular case of non-uniform acute irradiation (one part of the body is shielded and the other one is unshielded). Therefore the number k of parts of the hematopoietic tissue exposed to different doses of acute irradiation is taken to be equal to two in the models on hand.

In these series of modeling simulations, the doses of irradiation of shielded and unshielded parts of the hematopoietic tissue, D_1 and D_2, are fixed, the dose D_1 being substantially lower than the dose D_2. The variation of the degree of non-uniformity of partial acute irradiation is simulated by the variation of the fraction Ω_2 of the mass of unshielded part of the hematopoietic tissue, the fraction Ω_1 of the mass of shielded part of the hematopoietic tissue being equal to $(1 - \Omega_2)$. To compare effectively the responses of the major hematopoietic lineages to uniform acute irradiation and to non-uniform (partial) acute irradiation, the dose D of uniform acute irradiation is taken to be equal to the averaged dose (i.e., the whole-body dose) of partial acute irradiation:

$$D = D_1(1 - \Omega_2) + D_2\Omega_2. \tag{2.36}$$

In the framework of the models, the minimal levels and the first-day levels of concentrations of blood cells in the major hematopoietic lineages after partial acute irradiation and after the respective uniform acute irradiation are computed at fixed values of doses D_1 and D_2 and at various values of the parameter Ω_2 ($0 \leq \Omega_2 \leq 1$), i.e., at various values of the whole-body dose D of partial acute irradiation and at the respective values of the dose of uniform acute irradiation D [Eq. 2.36]. The obtained modeling results are presented in Figs. 2.5, 2.6, 2.7, and 2.8.

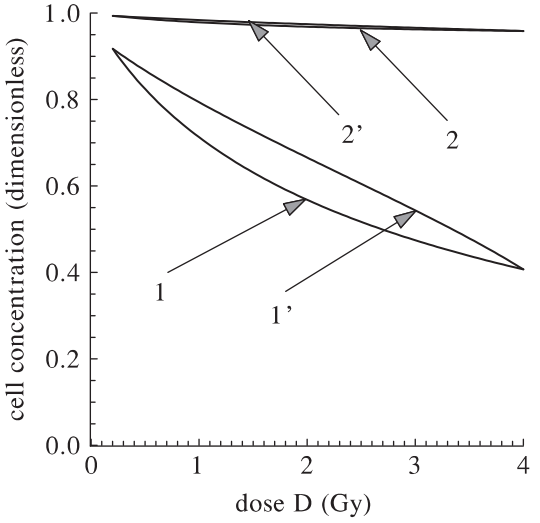

Fig. 2.5 The minimal levels and the first-day levels of the dimensionless concentration of blood thrombocytes (X_3 cells) in rodents (*mice*) after partial acute irradiation with various averaged doses D (*curves 1' and 2'*, respectively) and in mice after uniform acute irradiation with the same doses D (*curves 1 and 2*, respectively). Modeling results are computed at the fixed doses of irradiation of shielded and unshielded parts of the hematopoietic tissue (0.55 Gy and 11 Gy, respectively) and at various values of the parameter Ω_2, which specifies the fraction of the mass of unshielded hematopoietic tissue

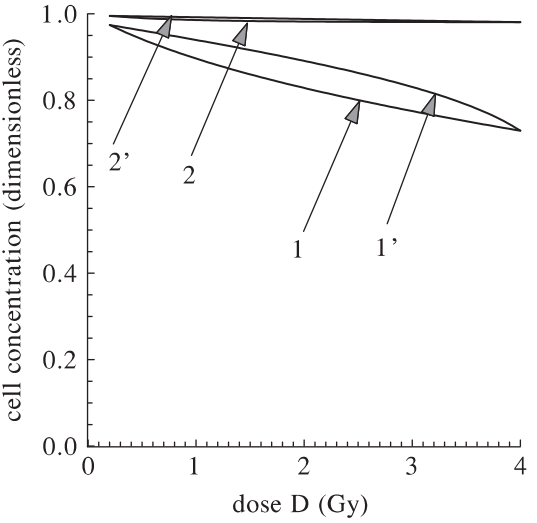

Fig. 2.6 The minimal levels and the first-day levels of the dimensionless concentration of blood erythrocytes (X_3 cells) in rodents (*rats*) after partial acute irradiation with various averaged doses D (*curves 1' and 2'*, respectively) and in rats after uniform acute irradiation with the same doses D (*curves 1 and 2*, respectively). Modeling results are computed at the fixed doses of irradiation of shielded and unshielded parts of the hematopoietic tissue (0.55 Gy and 11 Gy, respectively) and at various values of the parameter Ω_2, which specifies the fraction of the mass of unshielded hematopoietic tissue

As it follows from Figs. 2.5, 2.6, 2.7, and 2.8, the minimal levels and the first-day levels of concentrations of blood cells in the major hematopoietic lineages after partial acute irradiation and after the respective uniform acute irradiation are lower when the value of D is higher, i.e., when the parameter Ω_2 is larger. These modeling findings conform with experimental observations [13].

At fixed values of D, i.e., at fixed values of the parameter Ω_2 from the range $(0 < \Omega_2 < 1)$, the minimal levels of concentrations of the blood cells in the major hematopoietic lineages after partial acute irradiation are higher than those after uniform acute irradiation. In turn, at fixed values of D, i.e., at fixed values of the parameter Ω_2 from the range $(0 < \Omega_2 < 1)$, the first-day levels of concentrations of the blood cells in the thrombopoietic, erythropoietic, and granulopoietic systems after partial acute irradiation are slightly higher than those after uniform acute irradiation (Figs. 2.5, 2.6, and 2.7), whereas the first-day level of concentration of the blood lymphocytes in the lymphopoietic system after partial acute irradiation is considerably higher than that after uniform acute irradiation (Fig. 2.8). Obviously, in the case of the absence of shielding ($\Omega_2 = 1$) and in the case of the whole-body shielding ($\Omega_2 = 0$), these indices become equal to each other.

The obtained modeling results demonstrate that the lymphopoietic system is the most susceptible major hematopoietic lineage to both non-uniform (partial) acute irradiation and to uniform acute irradiation. Additionally, the differences

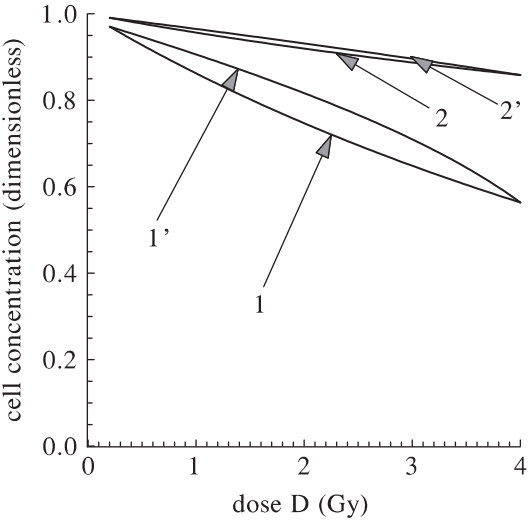

Fig. 2.7 The minimal levels and the first-day levels of the dimensionless concentration of blood granulocytes (X_3 cells) in rodents (*rats*) after partial acute irradiation with various averaged doses D (*curves 1' and 2'*, respectively) and in rats after uniform acute irradiation with the same doses D (*curves 1 and 2*, respectively). Modeling results are computed at the fixed doses of irradiation of shielded and unshielded parts of the hematopoietic tissue (0.55 Gy and 11 Gy, respectively) and at various values of the parameter Ω_2, which specifies the fraction of the mass of unshielded hematopoietic tissue

between the minimal levels of the concentration of blood cells in this major hematopoietic lineage and even between the first-day levels of concentration of these cells after non-uniform (partial) acute irradiation and after uniform acute irradiation (at the same whole-body doses of such exposures) are the most pronounced in the lymphopoietic system in comparison with those in the other major hematopoietic lineages. These modeling findings testify to the efficiency of the use of the first-day level of concentration of blood lymphocytes for the early predicting of the development of the lymphocytopenia after non-uniform (partial) acute irradiation.

2.5 Prognostic Importance of Lymphocytopenia After Partial Acute Irradiation

Partial acute irradiation is employed in the treatment of some form of cancer. The increase of the whole-body radiation dose received by patients in the course of such treatment can lead to the development of harmful reactions [14]. One of them is the development of leukopenia, which is the result of the development of granulocytopenia and/or lymphocytopenia. The former is characterized by the decrease of concentration of blood granulocytes up to dangerous levels, whereas

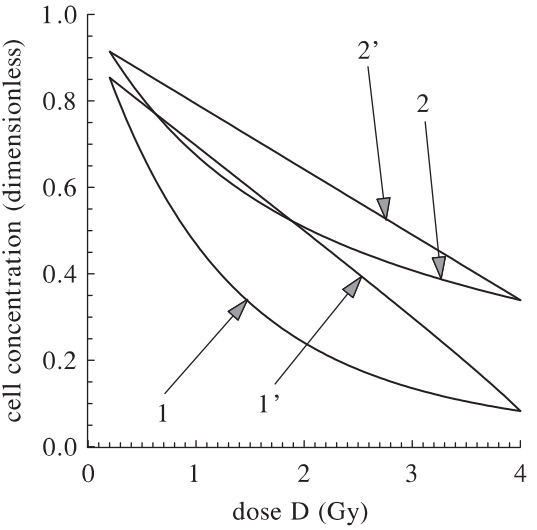

Fig. 2.8 The minimal levels and the first-day levels of the dimensionless concentration of blood lymphocytes (X_3 cells) in rodents (*rats*) after partial acute irradiation with various averaged doses D (*curves 1' and 2'*, respectively) and in rats after uniform acute irradiation with the same doses D (*curves 1 and 2*, respectively). Modeling results are computed at the fixed doses of irradiation of shielded and unshielded parts of the hematopoietic tissue (0.55 Gy and 11 Gy, respectively) and at various values of the parameter Ω_2, which specifies the fraction of the mass of unshielded hematopoietic tissue

the latter is characterized by the decrease of concentration of blood lymphocytes up to dangerous levels. The development of the leukopenia serves an indicator for the interruption of treatment. Therefore there is no doubt in a great practical significance of the prediction of the development of leukopenia after partial acute irradiation.

Interesting results of the experimental studies of peculiarities of radiation injury of two major hematopoietic lineages (the granulopoietic and lymphopoietic systems) after partial acute irradiation are presented in [14]. That work was devoted to the investigation of the early responses of these systems to partial acute irradiation, as well as to uniform acute irradiation. In the experiment, rodents (mice) were exposed to uniform acute gamma-irradiation and to three types of partial acute gamma-irradiation. In the case of uniform acute irradiation, the mass of unshielded part of the hematopoietic tissue was 100 % of its total mass, that corresponds to the parameter Ω_2 of 1.0 in the developed models. In the first case of partial acute irradiation, the mass of unshielded part of the hematopoietic tissue was 85 % of its total mass [14], that corresponds to the parameter Ω_2 of 0.85. In the second case of partial acute irradiation, when the front part of the body was exposed without shielding, the mass of unshielded part of the hematopoietic tissue was 54 % of its total mass [14], that corresponds to the parameter Ω_2 of 0.54. In the third case of partial acute irradiation, when the back part of the body was exposed without shielding, the mass of unshielded part of the hematopoietic tissue was 31 % of its

total mass [14], that corresponds to the parameter Ω_2 of 0.31. In [14], the dose D_2 of irradiation of unshielded part of the body was equal to 11 Gy, whereas the dose D_1 of irradiation of shielded part of the body was equal to 0.55 Gy. In experiments [14], the first-day levels of concentrations of functional blood cells in the granulopoietic and lymphopoietic systems in mice after the acute exposures listed above were examined.

The experimental data presented in [14] are used to verify the capability of the developed models of the granulopoietic and lymphopoietic systems to predict the first-day levels of concentrations of functional blood cells in these systems after partial acute exposures. For this purpose, the dynamics of the granulopoietic and lymphopoietic systems are computed in the framework of the developed models of these systems at the values of irradiation doses D_1 and D_2 of shielded and unshielded parts of an animal body, which were reported in [14], whereas the parameter Ω_2 is varied in the range ($0 \leq \Omega_2 \leq 1$).

As it follows from the obtained modeling results, the first-day levels of the dimensionless concentration of blood granulocytes after partial acute exposures and after uniform acute irradiation are equal to 0.9728, 0.9618, 0.9471, and 0.9400, when the values of parameter Ω_2 are taken the same as those in experiments [14], namely 0.31, 0.54, 0.85, and 1.00, i.e., when the values of parameter D [Eq. (2.36)] are equal to 3.79 Gy, 6.19 Gy, 9.43 Gy, and 11.00 Gy, respectively. The obtained modeling results imply that the first-day levels of blood granulocyte concentration 1 day after the considered exposures are close enough to the norm. These modeling predictions are consistent with experimental observations [14].

Figure 2.9 shows the first-day levels of the concentration of blood lymphocytes in the lymphopoietic system in mice after partial acute irradiation and after uniform acute irradiation, which are computed at the aforementioned values of doses D_1 and D_2 and at the values of parameter Ω_2 varied from zero to unity. Note that the case of $\Omega_2 = 0$ corresponds to uniform acute irradiation with the dose D_1, whereas the case of $\Omega_2 = 1$ corresponds to uniform acute irradiation with the dose D_2. Figure 2.9 also displays the experimental data [14] on the concentration of blood lymphocytes measured 1 day after four types of radiation exposure specified above.

As it follows from the modeling results, the first-day levels of the dimensionless concentration of blood lymphocytes after partial acute exposures and after uniform irradiation are equal to 0.583, 0.426, 0.216, and 0.114, when the values of parameter Ω_2 are equal to 0.31, 0.54, 0.85, and 1.00, i.e., when the values of parameter D are equal to 3.79 Gy, 6.19 Gy, 9.43 Gy, and 11.00 Gy, respectively. The corresponding experimental values of the first-day levels of the dimensionless concentration of blood lymphocytes are equal to 0.57 ± 0.13, 0.37 ± 0.13, 0.14 ± 0.10, and 0.12 ± 0.06 [14]. Thus, the modeling results are in a good agreement with those experimental data. The obtained agreement between modeling predictions and the respective experimental data [14] testifies to the capability of the lymphopoiesis model of predicting the first-day level of blood lymphocyte concentration after partial acute irradiation. In turn, this level can be used in the early prediction of the development lymphocytopenia after such radiation exposures.

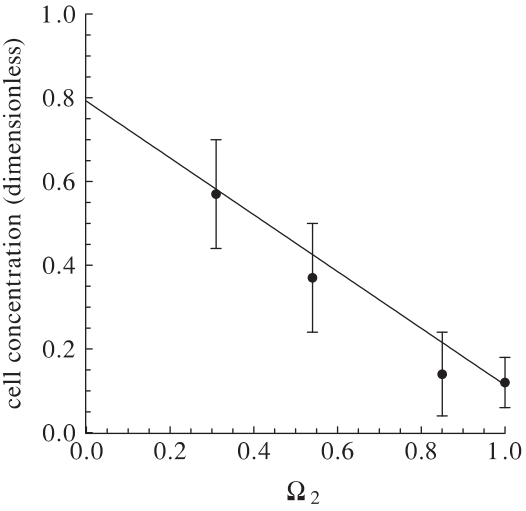

Fig. 2.9 The dependence of the first-day level of the dimensionless concentration of blood lymphocytes (X_3 cells) in rats after partial acute irradiation on the parameter Ω_2, which specifies the fraction of the mass of unshielded hematopoietic tissue. The modeling results (*curve*) are computed at $0 \leq \Omega_2 \leq 1$ and at the fixed doses of irradiation of shielded and unshielded parts of the hematopoietic tissue (0.55 Gy and 11 Gy, respectively). The relevant experimental data [14] are given by mean values of dimensionless concentration of blood lymphocytes (*circles*) in the aforementioned time moment and by mean square deviations from these mean values

2.6 Conclusions

Biologically motivated mathematical models of the dynamics of the major hematopoietic lineages (the thrombopoietic, erythropoietic, granulopoietic, and lymphopoietic systems) in mammals (rodents) exposed to non-uniform acute irradiation are developed and thoroughly investigated. These models are based on the mathematical models, which are capable of predicting the dynamics of these systems in mammals (rodents) exposed to uniform acute irradiation in a wide dose range (see Chap. 1).

The developed models account for the principal stages of development of hematopoietic cells. They also consider the general and specific regulatory mechanisms in the major hematopoietic lineages. The models are the systems of nonlinear ordinary differential equations, whose variables and constant parameters have clear biological meaning. A new element of these models is the consideration of non-uniform acute irradiation of the hematopoietic tissue as a composition of a certain number of uniform acute irradiations of its parts. The variable parameters of the models are the number of considered parts of the hematopoietic tissue, the fractions of masses of the considered parts of the hematopoietic tissue, and the doses of acute irradiation, which these parts of the hematopoietic tissue are exposed to.

The developed models are employed to compare the dynamics of the major hematopoietic lineages (the thrombopoietic, erythropoietic, granulopoietic, and lymphopoietic systems) in mammals (rats, mice) after non-uniform and uniform acute irradiation. It is found that the models reproduce the experimentally observed smaller depletion of the major hematopoietic lineages and their faster recovering after non-uniform acute irradiation than those after uniform acute irradiation at the same whole-body doses of these exposures. The obtained modeling results imply that the lesser injury and the faster recovery of the major hematopoietic lineages after non-uniform acute irradiation than those after uniform acute irradiation at the same whole-body doses of these exposures are due to higher levels of concentrations of the undamaged bone marrow precursor cells capable of dividing (X_1^{ud} cells) left in these systems after non-uniform acute irradiation than those after uniform acute irradiation. Taking into account that the compartment of X_1^{ud} cells includes undamaged stem cells and their undamaged committed progenies capable of dividing, the obtained modeling findings testify to the principal role of these cells in the processes running in the major hematopoietic lineages after non-uniform and uniform acute irradiation. Additionally, the modeling findings testify to inefficiency of the employment, for the prognostic purposes, of the whole-body dose D of partial acute irradiation.

The developed models are also used to study, in detail, the dynamics of the major hematopoietic lineages in mammals (rats, mice) after uniform acute irradiation and after partial acute irradiation, at which one part of the body and, hence, of the hematopoietic tissue is shielded and an other one is not shielded. In the framework of the models, the minimal levels and the first-day levels of concentrations of blood cells in the major hematopoietic lineages after partial acute irradiation and after uniform acute irradiation with equal values of the whole-body doses are computed, the doses of shielded and unshielded parts of the hematopoietic tissue being fixed and the fraction of mass of unshielded part being varied from zero to unity. It is revealed that the models provide the description of a deeper postirradiation injury of the major hematopoietic lineages in the rodents exposed to partial acute irradiation, when the mass of unshielded part of the hematopoietic tissue is larger, i.e., when the whole-body dose of partial acute irradiation is higher. The models also provide the description of a deeper postirradiation injury of the major hematopoietic lineages in the rodents exposed to uniform acute irradiation, when the dose of such exposure is higher. The modeling results also demonstrate that the lymphopoietic system is the most susceptible major hematopoietic lineage to both uniform and non-uniform (partial) acute irradiation.

Additionally, the models predict lesser depletions of the hematopoietic lineages after partial acute irradiation than those after uniform acute irradiation at equal whole-body doses of such exposures. Distinctions between the minimal levels and even between the first-day levels of the concentrations of the functional blood cells in the major hematopoietic lineages after partial acute irradiation and after uniform acute irradiation at the same whole-body doses of such exposures are the most pronounced in the lymphopoietic system. In other words, the lymphopoietic system is the most susceptible major hematopoietic lineage to the non-uniformity of acute

irradiation. Moreover, the modeling finings testify to the efficiency of the use of the first-day level of concentration of blood lymphocytes for the early predicting of the development of the lymphocytopenia after partial acute irradiation.

The developed models of the lymphopoietic and granulopoietic systems are used to simulate the responses of these major hematopoietic lineages to non-uniform (partial) acute irradiation and to uniform acute irradiation reported in [14]. The experimental work [14] was devoted to the investigation of early responses of the lymphopoietic and granulopoietic systems in rodents (mice) to uniform acute gamma-irradiation and to three types of partial acute gamma-irradiation. It is found that the first-day levels of the blood granulocyte concentration after the aforementioned exposures, which were predicted by granulopoiesis model, slightly deviate from its normal level, that conforms with experimental observation [14]. In turn, the first-day levels of the blood lymphocyte concentration after the aforementioned exposures, which were predicted by lymphopoiesis model, strongly deviate from its normal level. The modeling results are in a very good agreement with experimental data. The obtained agreement between modeling predictions and experimental data [14] testifies to the capability of the lymphopoiesis model of predicting the first-day level of blood lymphocyte concentration after partial acute irradiation. In turn, this level can be used in the early prediction of the development of the lymphocytopenia after partial acute irradiation.

The obtained modeling results bear witness to the validity of employment of the developed models of the major hematopoietic lineages in studies and predictions of the effects of non-uniform acute irradiation, including partial acute irradiation, on these systems in rodents (rats, mice), as well as in planning new experiments.

It is worthwhile to note that the employment of the developed mathematical model is limited to the modeling studies of the effects of non-uniform acute irradiation on the major hematopoietic lineages in rodents (mice, rats). At the same time, the proposed approach, which was successfully used to develop the models capable of describing the effects of non-uniform acute irradiation on the dynamics of the major hematopoietic lineages in rodents, can also be used to develop the mathematical models, which describe the effects of non-uniform acute irradiation on the dynamics of these systems in humans. In this case, the recently developed mathematical models (see Chap. 7, as well as [15–20]), which describe the effects of uniform acute/chronic irradiation on the dynamics of the major hematopoietic lineages in humans, form a basis of this approach. The models of the dynamics of the major hematopoietic lineages in humans exposed to non-uniform acute irradiation could be applied to predict the radiation injury of the hematopoietic system in individuals underwent to non-uniform acute exposures in radiation incidents and radiation accidents, as well as in the course of radiotherapy. Such modeling results would provide a better understanding of the risks to health from non-uniform irradiation and could help to elaborate an appropriate methods of their treatment. These models could also be helpful in the assessment of the radiation risks for the health of astronauts in cases of their exposures to non-uniform irradiation caused by solar particle events and in the development of operational countermeasures for them in long-term space missions.

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