Modeling a Radiotherapy Clinical Procedure: Total Body Irradiation

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Leukemia, non-Hodgkin's lymphoma, and neuroblastoma patients prior to bone marrow transplants may be subject to a clinical radiotherapy procedure called total body irradiation (TBI). To mimic a TBI procedure, we modified the Jones model of bone marrow radiation cell kinetics by adding mutant and cancerous cell compartments. The modified Jones model is mathematically described by a set of *n* + 4 differential equations, where *n* is the number of mutations before a normal cell becomes a cancerous cell. Assuming a standard TBI radiotherapy treatment with a total dose of 1320 cGy fractionated over four days, two cases were considered. In the first, repopulation and sub-lethal repair in the different cell populations were not taken into account (model I). In this case, the proposed modified Jones model could be solved in a closed form. In the second, repopulation and sub-lethal repair were considered, and thus, we found that the modified Jones model could only be solved numerically (model II). After a numerical and graphical analysis, we concluded that the expected results of TBI treatment can be mimicked using model I. Model II can also be used, provided the cancer repopulation factor is less than the normal cell repopulation factor. However, model I has fewer free parameters compared to model II. In either case, our results are in agreement that the standard dose fractionated over four days, with two irradiations each day, provides the needed conditioning treatment prior to bone marrow transplant.**Partial support for this research was supplied by the NIH-RISE program, the LSAMP-Puerto Rico program, and the University of Puerto Rico-Humacao. [*P R Health Sci J 2010;3:293-298*]**

Key words: Carcinogenesis mathematical model, Total body irradiation, Jones Model, Survival curves and cancerous cell populations

Radiotherapy is the use of X-rays, gamma rays, or electron or proton beams to treat cancer. The aim of the treatment is to kill the cancer cells, either directly or indirectly (i.e., by interfering with cell reproduction). There are two main types of radiotherapy treatment: external and internal radiotherapy. In external radiotherapy, a linear accelerator is used to deliver the radiation dose. Internal radiotherapy is where the source of radioactivity is put inside the human body so that it can get close to the cancerous tumor. Cancer patients usually undergo external radiotherapy in small doses; each dose is called a fraction. Dose fractionating reduces toxicity to normal tissues. The length of the radiotherapy treatment depends on the type of cancer. A procedure called Total Body Irradiation (TBI) is considered a special case in radiotherapy. This is because the treatment field is the entire body, and thus, the irradiated volume is highly irregular in shape.

TBI is used to treat leukemia, non-Hodgkin's lymphoma, and neuroblastomas and as a preparatory regimen prior bone marrow transplant. Patients usually receive a total dose between 10 to 12 Gy in eight fractions over four days, with at least six hours between fractions. As pointed out by an anonymous referee, TBI is only part of the conditioning regimen in the bone marrow transplant process. The most common pretreatment conditioning is a combination of chemotherapy and TBI. Before TBI, very high doses of chemotherapy are given to render the patient in remission, virtually cancer free. In this case, the main purpose of TBI is to help wipe out the host's marrow as well as reduce the probability of rejection. However, in some forms

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of leukemia, TBI is used to kill the remaining cancerous cells, thereby allowing donor marrow to engraft. For this reason, the hypothetical clinical case to be considered was a leukemia patient in whom the chemotherapy treatment prior to TBI had killed 90% of the patient's cancer cell population.

At this point, we posed three queries. First, is it possible to develop a quantitative model to reproduce the expected results of a TBI procedure? Second, are the supralethal doses used in TBI strong enough to suppress normal cells' sub-lethal repair and their repopulation among normal, mutated, and cancerous cells? Third, we wanted to investigate whether or not the standard delivery of the TBI dose over a period of four days, with six or eighteen hours between doses, is indeed ideal for the elimination of the remaining cancer cell populations.

To explore possible answers for the proposed queries, we modified the Jones et al. model (1-2) of bone marrow radiation cell kinetics. Originally, in this study, continuously irradiated stem-cell populations were modeled quantitatively by a three-compartmental formulation. However, Jones et al.'s cell kinetic model does not include possible mutations when ionizing radiation is acting on a cell population. Since DNA will not always be correctly repaired, the appearance of a mutation cannot be ignored. In fact, numerous studies have accumulated evidence of the cause-effect relationship between damage to DNA and the mutagenic effects of ionizing radiation. Therefore, in the proposed modified Jones model, it is assumed that n mutations will occur before a normal cell becomes a cancer cell. As a consequence, the number of compartments and the set of differential equations to mathematically describe the evolution in time of normal, injured, mutated, killed, and cancer cell populations increased from 3 to $n + 4$.

When sub-lethal repair and repopulation are not taken into consideration, the set of $n + 4$ differential equations can be solved in a closed form. We explicitly found exact solutions for $n = 1$ and $n = 2$. However, when sub-lethal repair and repopulation are considered, the corresponding set of differential equations can only be solved numerically.

In this paper, we used the proposed modified Jones model to mimic a TBI radiotherapy procedure. Two cases were considered. First, we postulated a TBI procedure in which repopulation and sub-lethal repair were not considered (model I), and thus, could be solved in a closed form. Next, this assumption was dropped, and a TBI procedure in which repopulation and sub-lethal are considered was numerically solved (model II).

Methods

The behavior of an irradiated stem-cell population can be schematized (Figure 1). Namely, at any time t, there is a normal cell population, $N_n(t)$; an injured cell population $N_i(t)$; n different mutant cell populations $N_{mj}(t)$, (j = 1, 2, … n); a killed cell population $N_k(t)$; and a cancerous cell population $N_c(t)$. Each of λ's parameters connecting compartments is associated with a biological process.

The dotted line in Figure 1 indicates other possible mutations. In Table 1, the different biological processes associated with the parameters of λ are explicitly given.

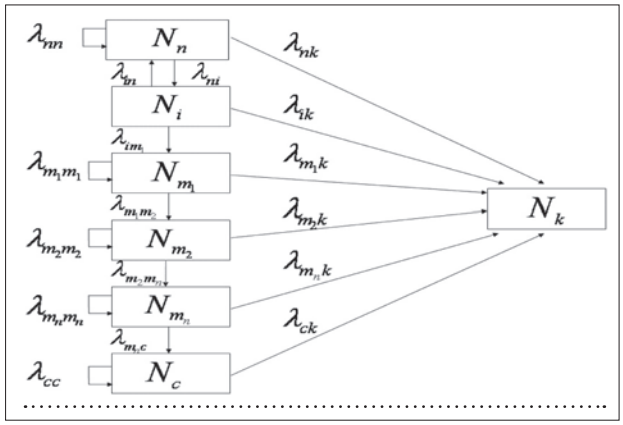

Figure 1. Schematic of the behavior of an irradiated stem-cell population.

Table 1. The biological processes associated with the parameters of λ as seen in Figure 1.

Parameter	Cellular Process
λ_{ni}	Sub-lethal Damage
λ_{in}	Repair of Sub-lethal Damage
λ_{nk}	1 hit killing
λ_{ik}	2 hit killing
λ_{nn}	Normal Cell Repopulation
$\lambda_{m_jm_j}$ $(j = 1,\ldots,n)$	Mutant Cell Repopulation
λ_{im_1}	No DNA Repair or Incomplete Repair
$\lambda_{m_jm_{j+1}}$ $(j = 1,\ldots,n-1)$	n Mutation
λ_{m_nc}	Mutant Cell → Cancer Cell
λ_{cc}	Cancer Cell Repopulation

The number of mutations required for a normal cell to become a cancer cell has been estimated by Renan (3) to be between two and ten. However, Little (4) and Wheldon (5) argue that most of the essential features of a carcinogesis model can be captured with $n = 2$.

Therefore, for $n = 2$ mutations, the dynamics of the carcinogenesis mathematical model schematized in Figure 1 can be described by a set of six differential equations. They are

$$\frac{dN_n}{dt} = -\lambda_{nk} N_n \frac{dD}{dt} - \lambda_{ni} N_n \frac{dD}{dt} + \lambda_{in} F_{in} N_i + \lambda_{nn} N_n M_n F_{nn}, \quad (1)$$

$$\frac{dN_i}{dt} = -\lambda_{ik} N_i \frac{dD}{dt} + \lambda_{ni} N_n \frac{dD}{dt} - \lambda_{im_1} N_i \frac{dD}{dt} - \lambda_{in} N_i F_{in}, \quad (2)$$

$$\frac{dN_k}{dt} = \lambda_{nk} N_n \frac{dD}{dt} + \lambda_{ik} N_i \frac{dD}{dt} + \lambda_{m_1 k} N_{m_1} \frac{dD}{dt} + \lambda_{m_2 k} N_{m_2} \frac{dD}{dt} + \lambda_{ck} N_c \frac{dD}{dt}, \quad (3)$$

$$\frac{dN_{m_1}}{dt} = -\lambda_{m_1 k} N_{m_1} \frac{dD}{dt} - \lambda_{m_1 m_2} N_{m_1} \frac{dD}{dt} + \lambda_{im_1} N_i \frac{dD}{dt} + \lambda_{m_1 m_1} N_{m_1} M_{m_1} F_{m_1 m_1}, \quad (4)$$

$$\frac{dN_{m_2}}{dt} = -\lambda_{m_2 k} N_{m_2} \frac{dD}{dt} - \lambda_{m_2 c} N_{m_2} \frac{dD}{dt} + \lambda_{m_1 m_2} N_{m_1} \frac{dD}{dt} + \lambda_{m_2 m_2} N_{m_2} M_{m_2} F_{m_2 m_2}, \quad (5)$$

$$\frac{dN_c}{dt} = -\lambda_{ck} N_c \frac{dD}{dt} + \lambda_{m_2 c} N_{m_2} \frac{dD}{dt} + \lambda_{cc} N_c M_c F_{cc}, \quad (6)$$

where D is the dose and M_n, M_{n_1}, M_{n_2}, M_c are the mitosis factors of normal, mutated, and cancerous cells, respectively. Further, $F_{in} = 2 - N_n - N_i$ and $F_{nn} = (1 - N_n - N_i) F_{in}$ represents dynamic factors that modify the normal cell repair (F_{in}) and proliferation rates (F_{nn}). In an analogous manner, we have defined and $F_{m_1 m_1}$, $F_{m_2 m_2}$ and F_{cc} to be the dynamic factors associated with the repopulation of both the first and second mutations and of cancerous cells, respectively.

Results

Exact Solutions

Equations 1 – 6 can be solved in an exact closed form when neither repopulation nor sub-lethal repair is considered. Thus, for $n = 1$ mutation, we obtain

$$N_n = C_1 e^{-D\lambda_1}, \quad (7)$$

$$N_i = \frac{\lambda_{ni} C_1 e^{-D\lambda_1}}{(\lambda_2 - \lambda_1)} + C_2 e^{-D\lambda_2}, \quad (8)$$

$$N_{m_1} = \frac{\lambda_{im_1} \lambda_{ni} C_1 e^{-D\lambda_1}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{\lambda_{im_1} \lambda_{ni} C_2 e^{-D\lambda_2}}{(\lambda_3 - \lambda_2)} + C_3 e^{-D\lambda_3}, \quad (9)$$

$$N_{m_1} = \lambda_{m_1 c} \left(\frac{\lambda_{ni} \lambda_{im_1} C_1 e^{-D\lambda_1}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)\lambda_4} + \frac{\lambda_{im_1} C_2 e^{-D\lambda_2}}{(\lambda_3 - \lambda_2)\lambda_5} + \frac{C_3 e^{-D\lambda_3}}{\lambda_6} \right) + C_4 e^{-D\lambda_{ck}}, \quad (10)$$

and in the above, C_1, C_2, C_3, and C_4 are constants, and

$$\lambda_1 = \lambda_{ni} + \lambda_{nk}, \quad (11)$$
$$\lambda_2 = \lambda_{im_1} + \lambda_{ik}, \quad (12)$$
$$\lambda_3 = \lambda_{m_1 c} + \lambda_{m_1 k}, \quad (13)$$
$$\lambda_4 = \lambda_{ck} + \lambda_1, \quad (14)$$
$$\lambda_5 = \lambda_{ck} + \lambda_2, \quad (15)$$
$$\lambda_6 = \lambda_{ck} + \lambda_3, \quad (16)$$

where N_k can be obtained from $1 - Nn - Ni - N_{m_1} - N_{m_2} - N_c$. For $n = 2$ mutations, N_n, N_i, and N_{m_1} are the same as those for $n = 1$ mutation. The remaining solutions are

$$N_{m_2} = \lambda_{m_1 m_2} \left(\frac{\lambda_{ni} \lambda_{im_1} C_1 e^{-D\lambda_1}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)(\lambda_4 - \lambda_1)} + \frac{\lambda_{im_1} C_2 e^{-D\lambda_2}}{(\lambda_3 - \lambda_2)(\lambda_4 - \lambda_2)} + \frac{C_3 e^{-D\lambda_3}}{(\lambda_4 - \lambda_3)} \right) + C_4 e^{-D\lambda_4}, \quad (17)$$

$$N_c = \lambda_{m_2 c} [\lambda_{m_1 m_2} (\lambda_{im_1} (\frac{\lambda_{ni} C_1 e^{-D\lambda_1}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)(\lambda_4 - \lambda_1)\lambda_5} + \frac{C_2 e^{-D\lambda_2}}{(\lambda_4 - \lambda_2)(\lambda_3 - \lambda_2)\lambda_6}) + \frac{C_3 e^{-D\lambda_3}}{(\lambda_4 - \lambda_3)\lambda_7}) + \frac{C_4 e^{-D\lambda_4}}{\lambda_8}] + C_5 e^{-D\lambda_{ck}}, \quad (18)$$

where, in the above, λ_1 and λ_2 have the same meaning, as in the case of $n = 1$ mutation. The remaining parameters, λ_3, λ_4, λ_5, λ_6, λ_7, and λ_8, are defined for $n = 2$ mutations, as follows

$$\lambda_3 = \lambda_{m_1 m_2} + \lambda_{m_1 k}, \quad (19)$$
$$\lambda_4 = \lambda_{m_2 c} + \lambda_{m_2 k}, \quad (20)$$
$$\lambda_5 = \lambda_{ck} + \lambda_1, \quad (21)$$
$$\lambda_6 = \lambda_{ck} + \lambda_2, \quad (22)$$
$$\lambda_7 = \lambda_{ck} + \lambda_3, \quad (23)$$
$$\lambda_8 = \lambda_{ck} + \lambda_4, \quad (24)$$

notice that parameters λ_3, λ_4, λ_5, and λ_6 illustrated by equations 19-22 are not the same as those defined for $n = 1$ mutation. The solution for N_k can be obtained in the same way as mentioned before. Notice that it is easy to generalize the above results for $n > 2$.

Interestingly, equation 10 suggests that a cancer cell population could be initiated with just one mutation. The cancer cell population will not depend only on $\lambda_{m_n c}$, but also on the product of all the "decaying parameters" ($\lambda_{in} \lambda_{im_1} \lambda_{m_1 m_2} \lambda_{m_2}$ for two mutations). There are also constraints on the values of the parameters of λ. For example, for two mutations, $\lambda_2 - \lambda_1 \neq 0$, $\lambda_3 - \lambda_1 \neq 0$, $\lambda_4 - \lambda_1 \neq 0$, etc.

Numerical Solutions

Next, we numerically solved equations 1-6. To do so, we needed to assign numerical values to all of the parameters of λ and to the repopulation dynamic factors for the normal, mutated, and cancerous cells. In Table 2, we listed the chosen numerical values for λ's parameters. The first five parameters in Table 2 are the resulting values for hematopoietic stem cells receiving 22 MeV of radiation, extrapolated from animal data to men by Morris et al. (6). The remaining values in Table 2 were estimated as follows. The λs-rate constants that mediate movement of cells between the normal, mutated, and cancerous compartments to the killed compartment were set to the same value.

Also, it was assumed that $\lambda_{in} = \lambda_{im_1}$, $\lambda_{m_1 m_2} = \lambda_{m_2 c}$ and $F_{m_1 m_1} = \alpha F_{nn}$, $F_{m_2 m_2} = \beta F_{nn}$ $F_{cc} = \gamma F_{nn}$, where α, β, and γ are dimensionless numbers. At any time t, we can expect that the mutant population is less than the population of the normal cells. Thus, for the plotting of Figures 2-7, we chose the following values: $\alpha = \beta = 0.5$. Usually, since the cancer cell-cycle time of cancer cells is shorter than that of normal cells, it is expected that $\gamma > 1$. However, TBI treatments affect cancer cells to a greater degree than they do normal cells; for that reason, we chose the following value: $\gamma = 0.5$. Note that for more realistic calculations α, β, and γ could be time-dependent. The dose rate depends on the cancer tumor, exposure time, and radiotherapy procedure.

Table 2. λ's numerical parameter values.

Parameters		Parameters	
λ_{ni}	6.4 x 10-3 cGy -1	$\lambda_{m_1m_2}$	6.42 x 10-3 cGy -1
λ_{in}	6.0 x 10-3 cGy -1	λ_{m_2c}	6.43 x 10-3 cGy -1
λ_{nk}	2.3 x 10-3 cGy -1	λ_{ck}	2.31 x 10-3 cGy -1
λ_{ik}	7.0 x 10-2 cGy -1	λ_{m_2k}	2.32 x 10-3 cGy -1
λ_{nn}	2.2 x 10-4 min-1	$\lambda_{m_1m_1}$	2.2 x 10-4 min-1
λ_{im_1}	6.41 x 10-3 cGy -1	$\lambda_{m_2m_2}$	2.2 x 10-4 min-1
λ_{m_1k}	2.31 x 10-3 cGy -1	λ_{cc}	2.2 x 10-4 min-1

Clinical Case: Total Body Irradiation

To test our proposed model, we considered a patient who had received (prior to TBI) a chemotherapy treatment that killed 90% of the original cancer cell population. As usual for TBI, the radiation dose was fractionated over several days. The total dose given to the cancer patient was 1320 cGy in 8 fractions over 4 days. Those fractions were 165 cGy delivered daily at 9:00 am and 3:00 pm. The dose rate was 14.2 cGy/min, and the exposure time was 11.6 min.

Figures 2-4, show (for model I) the behavior of the survival curve ($S = N_n + N_i + N_{m_1} + N_{m_2}$) and the killed/cancer cell populations, respectively.

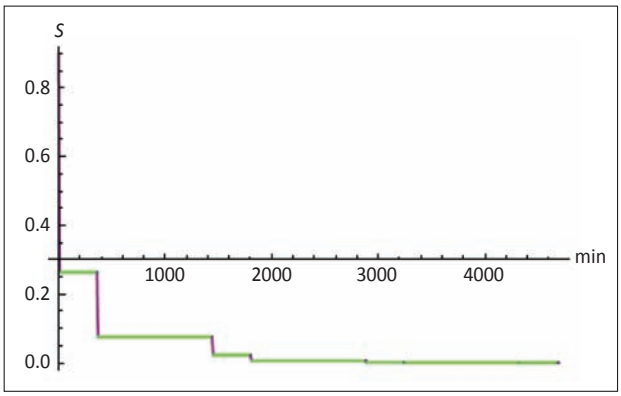

Figure 2. The survival curve ($S = N_n + N_i + N_{m_1} + N_{m_2}$) for model I.

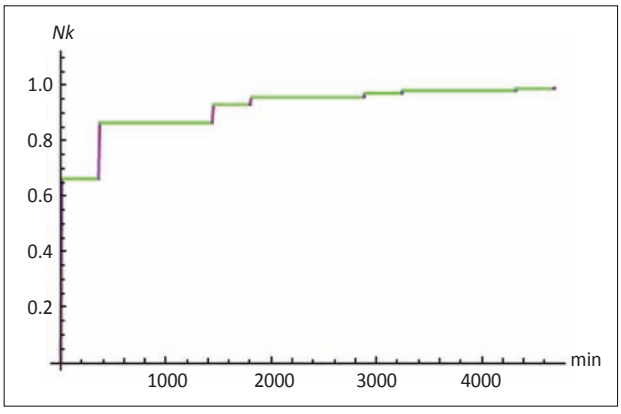

Figure 3. The killed cell population for model I.

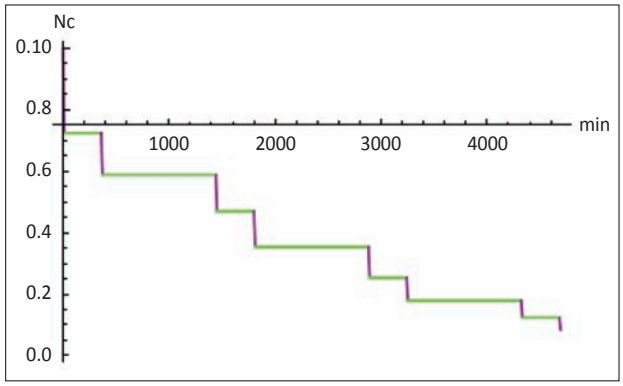

Figure 4. The cancer cell population for model I.

In Figures 5-7, we show a comparison between model I (purple and green) and model II (red and blue). As expected, Figures 5-7 demonstrate that the survival curve and the killed and cancer cell populations are greater when repopulation and sub-lethal repair are considered.

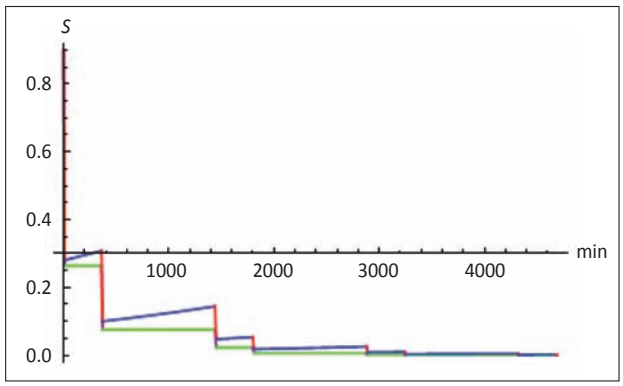

Figure 5. Survival curves for model I (purple and green) and model II (blue and red).

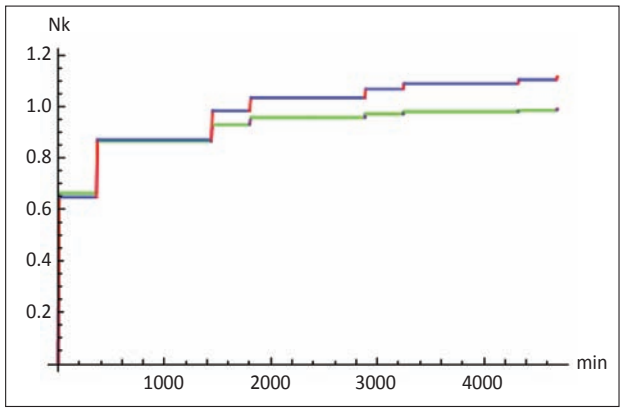

Figure 6. Killed cell populations for model I (purple and green) and model II (blue and red).

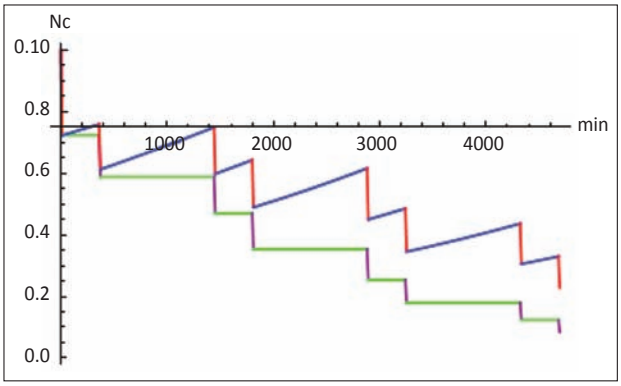

Figure 7. Cancer cell populations for model I (purple and green) and model II (blue and red).

Conclusions

In this study, we developed a modified Jones model with n = 2 mutations in order to ascertain the evolution in time of survival curves and cancerous and killed cell populations during a TBI clinical procedure. Two cases (model I and model II) were considered. First, in model I, we took neither repopulation nor sub-lethal repair into consideration and solved, in a closed form, the resulting set of differential equations. Second, in model II, repopulation and sub-lethal repair were considered, and the set of non-linear differential equations was solved by implementing a computer code in MATHEMATICA 7.0 (www.wolframresearch.com).

At the end of the first irradiation day, the number of killed cells in models I and II was about the same. In the following irradiation days, the killed cell population was higher in model II than in model I. The opposite happened with the survival curves. Both models I and II, predicted correctly that at the end of the TBI treatment the survival curves would reach zero.

Regarding the cancer cell population, as expected, it was greater in model II than in model I for each of the four days of treatment. Notice also, that at the end of the TBI treatment, model I and model II both predicted the eradication of most of the cancer cell population. However, to reach this result with model II, we had to set $\gamma = 0.5$, i.e., the cancer cell repopulation factor would be less than the normal cell repopulation factor during a TBI procedure. In this regard, model I is better than model II because it has fewer free parameters.

Finally, although it is not shown here, we modified the initial conditions to those of a TBI treatment and solved the respective differential equations that define models I and II. We can confirm that, qualitatively for all trials, the same conclusions were reached and held true.

In summary, the three queries posed at the beginning of this paper are now answered. First, a quantitative model to mimic a TBI clinical procedure has been developed and hypothetically tested. As far as know, the proposed quantitative model is new in the literature. It can be easily modified for use in other TBI treatments with different protocols, i.e., different doses, days fractionated, or number of irradiations per day. Second, it seems that during a TBI procedure, the repopulation and sub-lethal repair of normal, mutated, and cancerous cell populations is nearly suppressed. Third, the simulation of the TBI procedure proved that the standard clinical treatment for bone marrow transplants is correct in terms of the number of fractionated doses, the number of days, and the exposure time.

Resumen

Previo a un trasplante de medula ósea, pacientes con leucemia, linfoma no-Hodgkin, y neuroblastoma podrían ser sometidos a un procedimiento en radioterapia llamado Radiación Total del Cuerpo (RTC). Para simular RTC hemos modificado el modelo de Jones, añadiendo compartimientos virtuales para las poblaciones de células mutantes y cancerosas. Este modelo de Jones modificado es descrito matemáticamente por un conjunto de *n+4* ecuaciones diferenciales, donde n es el número de mutaciones antes de que la célula normal se transforme en una célula cancerosa. Asumiendo un procedimiento común de radioterapia RTC, con una dosis total de 1320 cGy fraccionada en cuatro días, dos casos son considerados. Primero, el modelo I es definido cuando la repoblación y reparación del daño subletal no son tomados en cuenta. Se demuestra en este caso, que el modelo de Jones modificado puede ser resuelto en forma exacta. Segundo, si la repoblación y reparación del daño subletal son consideradas, entonces el modelo de Jones modificado puede ser sólo resuelto numéricamente (modelo II). Luego de un análisis grafico y numérico, podemos concluir que se pueden reproducir los resultados esperados para un tratamiento RTC usando el modelo I. El modelo II, puede también ser utilizado sólo si el factor de repoblación para las células cancerosas es menor que el factor de repoblación de las células normales. Sin embargo, el modelo I tiene menos parámetros libres que el modelo II. En cualquiera de los dos modelos estudiados, nuestros resultados sugieren que el tratamiento clínico usual, es decir el fraccionamiento de la dosis en cuatro días con dos irradiaciones diarias, provee el acondicionamiento adecuado para el trasplante de médula ósea.

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