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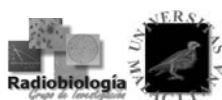
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Abstract

In this work is presented a dose-response model that let us make prediction on cell response under irradiation schemes in radionuclide therapy from an adaptation of radiobiological model proposed by Sanchez-Reyes [Radiat. Res., 1992;130:139-147] which considering that cell repair mechanisms could be saturated and it could be affected by radiation action. The dose rate was considered uniform spatially distributed changing exponentially respect on time. The contribution of cell proliferation was taken into account as a cell population with exponential growth. Close-form expressions were obtained to calculate the effective irradiation time (T_{eff}), effective dose (D_{eff}) and therapeutic efficacy (TE). The result were compared with linear-quadratic model (LQ) prediction at low dose rate considering the Lea-Catcheside's factor as modifying the quadratic term in LQ model in view of saturable repair model could show similar prediction of LQ model like occurs with other sublethal damage model which offers a mechanistic interpretation for LQ model. The model will produce similar result to those that could be obtained with LQ model at low dose rate. The formalism presented here let us to determine parameters that could be used in the prediction of irradiation response in radionuclide therapy with beta emitters.

Key words: dose-response model; radionuclide therapy; low dose rate; saturable-repair model

Introduction

In conventional radiotherapy (external radiotherapy, low dose rate and high dose rate brachytherapy) doses of about 60Gy are necessary to achieve the tumor control or eradication. For systemic applications in radionuclide radiotherapy the dose rate are often ranged in 0.1-0.5cGy/min and only total dose 15-20Gy could be reached with effective irradiation times of few days mainly when monoclonal antibodies had been used in order to accomplish a curative effect. Besides in radionuclide radiotherapy, the dose rate decreases as a monoexponential in whole body and biexponential in tumor and other compartments where the uptake and elimination phases are well differentiated both determined by the effective uptake and elimination times respectively. Many author had suggested that it is necessary an additional about a 20% higher dose than conventional radiotherapy because of dose rate effects [1,2]. The final biological response in radionuclide therapy will be determined not only by the total dose, but also by initial dose rate, the length of irradiation time (effective half-life) and biological factors like radiosensitivity, repair and doubling times. Ideal

conditions for to achieve the main goal in radionuclide radiotherapy in view of radionuclide that could be used had been formulated in previous works [2,3].

The cell response to irradiation is a non-passive complex biochemical process and its dose and dose rate-dependence had been demonstrated in several works [3,4]. Most quantitative models of radiation action on cells make the assumption that cell repair mechanisms are relevant in the response and it proceed in a dose-dependent way. The cell proliferation will influence the response to irradiation like cell repair/recovery when the overall irradiation is comparable or greater than cell population doubling time. In radionuclide radiotherapy often happens that the irradiation effective time is comparable to doubling time, and then it must be included into the model.

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The development in modern radiotherapy have been driven by the possibility of isoeffecting prediction for alternate irradiation schemes using radiobiological models which had been developed on the experiences in clinical and basic researches done on radiobiology for several years. Many proposal had been made to apply radiobiological model for the prediction of the treatment response in radionuclide radiotherapy in order to improve the treatment efficacy decreasing the complication of critical tissues like bone marrow, etc [5,6,7,8].

In general *saturation repair model* consider the movement of repair kinetics from an unsaturated state where substrate concentration (at low dose) is much small than the concentration of repair enzyme, to a state where both are comparable, and on to a totally saturated state where the enzyme concentration alone is rate limiting. Such a movement of the repair kinetics in competition with a damage fixation process could produce shouldered survival curves as are observed. Since only one type of lesion and single-hit killing are postulated the absence of any repair these lesion will produce an straight survival curve. The term *saturable repair* had been used by many author in the sense of chemical kinetics [9,10,11] or considering the influence of radiation on the repair process as function of the absorbed dose or dose rate [12]. Saturable repair models are able, in principle, to explain the usual data base of radiobiological phenomena including which where other biophysical model does not work good. Alternatively, features of this model could be combined into hybrid models.

We present here an analytical solution for the radiobiological model proposed by Sanchez-Reyes [12] adapted to be used in radionuclide therapy to calculate the survival fraction $S(t)$ in a cell population after irradiation. We considered that dose rate will change exponentially respect on time and it is uniform spatially distributed. The contribution of cell proliferation was taken into account as a cell population with exponential growth. Close-form expressions were obtained to calculate the effective irradiation time (T_{eff}), effective dose (D_{eff}) and therapeutic efficacy (TE). The result were compared with linear-quadratic model (LQ) prediction at low dose rate considering the Lea-Catcheside's factor as modifying the quadratic term in LQ model in view of saturable repair model could show similar prediction of LQ model like occurs with other *sublethal damage model* which offers a mechanistic interpretation for LQ model.

Material and methods

Sánchez-Reyes radiobiological model modified by proliferation

The radiobiological model proposed by Sanchez-Reyes considers a cell population where the DNA repair mechanisms are saturable and it could be affected by radiation action. The details of assumptions considered in the formulation of the model appeared in the work referred in [12]. The cell

proliferation contribution to the irradiation response could be considered by adding a term $\lambda S(t)dt$ in the equation to calculate $S(t)$ (see eq. (8) in [12]). It is supposed that cells growth exponentially what is agreed with small tumor. Transforming the system (8) in [12] by setting explicitly $r(t)$ into the equations we can obtain the new system,

$$dS(t) = -AS(t)[1 - B(t)]r(t)dt + \lambda S(t)dt \quad (1.1)$$

$$dB(t) = -\chi B(t)\exp[-\mu t]r(t)dt \quad (1.2)$$

where $r(t)$ is the dose rate function, $S(t)$ is the survival fraction at time t , A is the probability per unit dose that a cell in perfect working state changes into a damage state, $B(t)$ is the probability of repair which is function of dose and time, χ is the probability per unit dose that repair mechanism is affected by radiation and will dependent on LET radiation. As it is considered in [4] we have assumed here that repair function have an exponential form where μ is related to the mean repair time T_μ as $\mu=0.693/T_\mu$. The parameter λ is the cell proliferation rate and it is related to doubling time T_D as $\lambda=0.693/T_D$. At $t = 0$, it is considered that $B(t=0)=B_0$, $S(t=0)=1$.

The dose rate is considered spatially uniform distributed and its dependence with time will be given by:

$$r_B(t) = r_{0,ext} [\exp(-k_e t) - \exp(-k_u t)] \quad (2)$$

where $r_{0,ext}$ is the extrapolated initial dose rate, k_u and k_e are the effective uptake and elimination rate constants of activity in tumor. Both effective rates constants are related to the effective uptake and elimination times T_u and T_e as $k_u=0.693/T_u$ and $k_e=0.693/T_e$ respectively.

Results

Survival curves and effective irradiation time

The details for the solution of the equations system for the radiobiological model proposed by Sanchez-Reyes for low dose approximation and dose rate decaying sources will not discussed here. The solution of system (1.1)-(1.2) could be obtained from the integral:

$$\ln[S(t)] = -A \int_0^t \left\{ (1 - B(t))r_{0,ext} [\exp(-k_e t) - \exp(-k_u t)] \right\} dt + \lambda t \quad (3.1)$$

where

$$B(t) = B_0 \exp \left\{ -\chi r_{0,ext} \left[\frac{1}{\lambda_e} [1 - \exp(-\lambda_e t)] - \frac{1}{\lambda_u} [1 - \exp(-\lambda_u t)] \right] \right\} \quad (3.2)$$

is obtained by integration of (1.2), $\lambda_e = \mu + k_e$ and $\lambda_u = \mu + k_u$. Substituting (3.2) into (3.1), expanding as Taylor series of exponential terms that appear in (3.1) and rejecting the serial terms with order greater that 2 results:

$$\ln[S(t)] = -\alpha d(t) \left\{ 1 + \frac{2r_{0,ext}^2}{(\alpha/\beta)d(t)} \left[\tau_1^{SR}(t) - \tau_2^{SR}(t) - \tau_3^{SR}(t) \right] \right\} + \lambda t \quad (4.1)$$

where:

$$\tau_1^{SR}(t) = \left(\frac{1}{\lambda_e} - \frac{1}{\lambda_u} \right) \left\{ \frac{1}{k_e} [1 - \exp(-k_e t)] - \frac{1}{k_u} [1 - \exp(-k_u t)] \right\} \quad (4.2)$$

$$\tau_2^{SR}(t) = \frac{1}{\lambda_e} \left\{ \frac{1}{\lambda_e + k_e} [1 - \exp(-(\lambda_e + k_e)t)] - \frac{1}{\lambda_e + k_u} [1 - \exp(-(\lambda_e + k_u)t)] \right\} \quad (4.3)$$

$$\tau_3^{SR}(t) = \frac{1}{\lambda_u} \left\{ \frac{1}{\lambda_u + k_e} [1 - \exp[-(\lambda_u + k_e)t]] - \frac{1}{\lambda_u + k_u} [1 - \exp[-(\lambda_u + k_u)t]] \right\} \quad (4.4)$$

where $d_B(t)$ is the dose cumulated until time t calculated by time integration of equation (2.2). The constants α and β are defined by the equations (14)-(15) in [12] as $\alpha = A(1-B_0)$ and $\beta = \frac{1}{2}AB_0\chi$ for low dose rate approximation in the Sanchez-Reyes model. Making $k_u \rightarrow \infty$ we could obtain the appropriated expressions to calculate $\ln[S(t)]$ for monoexponential decay dose rate function. It will produce an expression for $\ln[S(t)]$ similar to equation (40) in [12].

It is known that when proliferation is considered into account there is an effective irradiation time that represent the period of time in which irradiation will be radiotoxic for the cell population. The effective irradiation time (T_{eff}^{SR}) could be calculate by differentiation of (4.1). Two assumption must be considered for $t \geq T_{eff}^{SR}$: (a) uptake phase is ended or $\exp(-k_u T_{eff}^{SR}) \approx 0$ and (b) all radiation damage is repaired at very low dose rate or $\exp(-\mu T_{eff}^{SR}) \approx 0$, then:

$$T_{eff}^{SR} = \frac{1}{k_e} \ln \left[\frac{r_{0,ext}}{\lambda/\alpha} \left(1 + \frac{2r_{0,ext}}{(\alpha/\beta)\lambda_e} \right) \right] \quad (5)$$

Figure 1 show the survival curve as time function calculated by expression (4.1). Substituting (5) in (4.1)-(4.4) we obtain the survival fraction at T_{eff}^{SR} that we called *effect* or S_{min} . For $t > T_{eff}^{SR}$ the net effect observed is the cell population growth.

The existence of T_{eff}^{SR} and S_{min} give us that there is a dose rate limit (r_{crit}^{SR}) that when $r < r_{crit}^{SR}$ the dose rate is insufficient to overcome the influence of cell growth. The r_{crit}^{SR} value may be obtained from eq.(5) since the term into crochets must be always greater than 1, then results that:

$$r_{crit}^{SR} = \left(\frac{\alpha}{\beta} \right) \left(\frac{\lambda_e}{2} \right) \left[\sqrt{1 + \frac{8(\lambda/\alpha)}{(\alpha/\beta)\lambda_e}} - 1 \right] \quad (6)$$

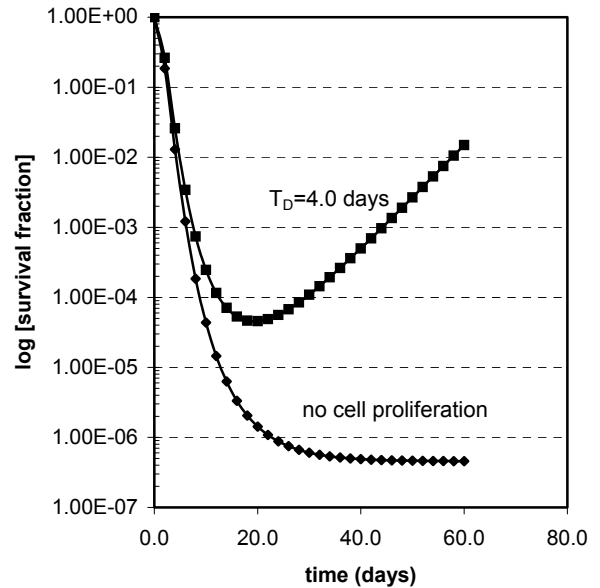


Figure 1. Survival curve calculated using the Sanchez-Reyes model adapted to be used in radionuclide therapy and including the contribution of cell proliferation. When cell proliferation is included there is an effective irradiation time T_{eff} , that $t > T_{eff}$ the dose is wasted because it do not overcome cell growth. Parameters: $T_u=1.0$ day, $T_e= 5.0$ days, $r_{0,ext}=0.5$ cGy/min, $T_D=4.0$ days, $T_\mu= 1.5$ hours, $\alpha/\beta= 10$ Gy, $\alpha=0.35$ Gy⁻¹.

Effective dose, therapeutic efficacy and dose response curves

Other implication when cell proliferation is considered is that only a fraction of total dose delivered will be useful in treatment. In a previous work O'Donoghue *et al* [4] introduced the concepts of *dose effective* (D_{eff}) as the fraction of total dose delivered which is lethal on cell population and *therapeutic efficacy* (TE) as the effective dose to total dose ratio that let us to evaluate the effectiveness of the total dose delivered. In our case, D_{eff} could be calculated substituting (5) in (4.1)-(4.4):

$$\ln[S(T_{eff}^{SR})] = \ln[S_{min}] = -\alpha D_{eff} \quad (7.1)$$

where

$$D_{eff} = r_{0,ext} \left(\frac{1}{k_e} - \frac{1}{k_u} \right) RE^{SR}(T_{eff}^{SR}) - \frac{r_{0,ext}}{k_e} RE^{SR}(T_{eff}^{SR}) \exp(-k_e T_{eff}^{SR}) - \frac{\lambda}{\alpha} T_{eff}^{SR} \quad (7.2)$$

$$RE^{SR}(T_{eff}^{SR}) = 1 + \frac{2r_{0,ext}^2}{(\alpha/\beta)d(T_{eff}^{SR})} \left[\tau_1^{SR}(T_{eff}^{SR}) - \tau_2^{SR}(T_{eff}^{SR}) + \tau_3^{SR}(T_{eff}^{SR}) \right] \quad (7.3)$$

where the $\tau_i^{SR}(T_{eff}^{SR})$ values are given by expression (4.2)-(4.4) evaluated for $t = T_{eff}^{SR}$. The radiobiological significance of each term in (7.2) was described by O'Donoghue *et al*, but in our expression will appear the magnitude $RE^{SR}(T_{eff}^{SR})$ which keeps into account the influence of repair in the cell population response. The last term in (7.2) is the additional dose given that is necessary to overcome cell proliferation to reach

the effect. Following the definition of TE we have obtained that:

$$TE = \frac{D_{eff}}{D_T} = 1 - \left(\frac{T_e}{\tau_c} \right) RE^{SR} (T_{eff}^{SR}) \exp(-k_c T_{eff}^{SR}) - \frac{\lambda/\alpha}{1.44 r_{0,ext} \tau_c} T_{eff}^{SR} \quad (8)$$

where $\tau_c = T_e - T_u$ and $D_T = 1.44 r_{0,ext} \tau_c$ is the total dose delivered that is calculated by integration of dose rate function given by (2) until complete source decay, T_e and T_u are the effective uptake and elimination times. The figure 2 shows the change in TE as function of $r_{0,ext}$ for slow and fast growing tumor.

Since the irradiation conditions will be driven by the extrapolated initial dose rate, as well as, the uptake and elimination effective times of activity in the tumor we can obtain dose-response curves for a cell population under irradiation varying the biokinetics parameters which driven the uptake and elimination processes. In the Figure 3 are shown curves of the cell population response to irradiation given by S_{min} as function of extrapolated initial dose rate and the biokinetics parameters.

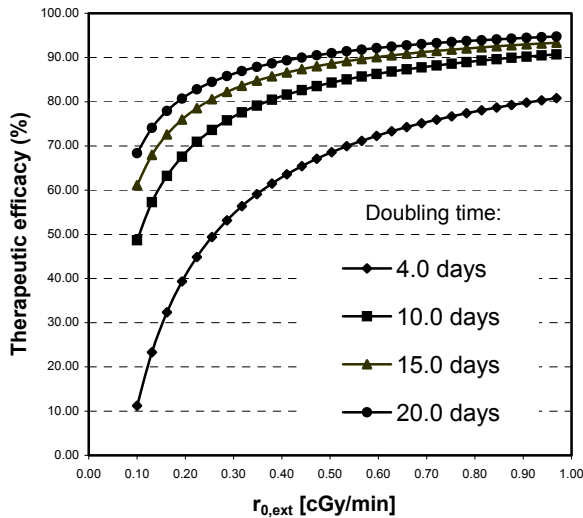


Figure 2. Dependence of TE as function of $r_{0,ext}$ obtained with Sanchez-Reyes model adapted to be used in radionuclide therapy and including the contribution of cell proliferation. **Parameters:** $T_u=1.0$ day, $T_e=5.0$ days, $r_{0,ext}=0.5$ cGy/min, $T_\mu=1.5$ hours, $\alpha/\beta=10$ Gy, $\alpha=0.35$ Gy⁻¹.

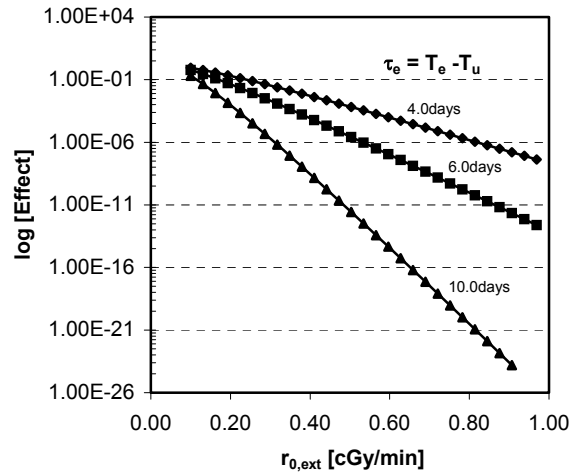


Figure 3. Dose-response curves as function of extrapolated initial dose rate obtained with Sanchez-Reyes' model including the contribution of cell proliferation to be used in radionuclide therapy. **Parameters:** $T_u=1.0$ day, $r_{0,ext}=0.5$ cGy/min, $T_D=4$ days, $T_\mu=1.5$ hours, $\alpha/\beta=10$ Gy, $\alpha=0.35$ Gy⁻¹.

Relations with linear-quadratic (LQ) model.

Linear-quadratic (LQ) model could be adapted when dose rate changed as a decaying source, like occurs for brachytherapy with decaying sources or continuous irradiation at low dose rate[13]. The expressions (7.2)-(7.3) are equivalent to those reported by González *et al* [14] for a LQ formulation adapted for radionuclide therapy:

$$\ln[S(t)] = -\alpha d(t) RE^{LQ}(t) + \lambda t \quad (10.1)$$

$$RE^{LQ}(t) = 1 + \frac{2r_{0,ext}^2}{(\alpha/\beta)d(t)} [\tau_1^{LQ}(t) - \tau_2^{LQ}(t) - \tau_3^{LQ}(t)] \quad (10.2)$$

$$\tau_1^{LQ}(t) = \frac{1}{2k_c(\mu - k_c)} \left[1 - \exp(-2k_c t) - 2 \frac{k_c}{\lambda_c} [1 - \exp(-\lambda_c t)] \right] \quad (10.3)$$

$$\tau_2^{LQ}(t) = \frac{1}{k_u} \left[\frac{1}{\mu - k_c} + \frac{1}{\mu - k_u} \right] [1 - \exp(-k_u t)] - \frac{k_u}{k_c} \left\{ \frac{1 - \exp(-\lambda_c t)}{\lambda_c(\mu - k_u)} + \frac{1 - \exp(-\lambda_u t)}{\lambda_u(\mu - k_c)} \right\} \quad (10.4)$$

$$\tau_3^{LQ}(t) = \frac{1}{2k_u(\mu - k_u)} \left[1 - \exp(-2k_u t) - 2 \frac{k_u}{\lambda_u} [1 - \exp(-\lambda_u t)] \right] \quad (10.5)$$

where $k_{eu} = k_e + k_u$. The effective irradiation time T_{eff}^{LQ} calculated using the LQ formulation above mentioned is given by [14]:

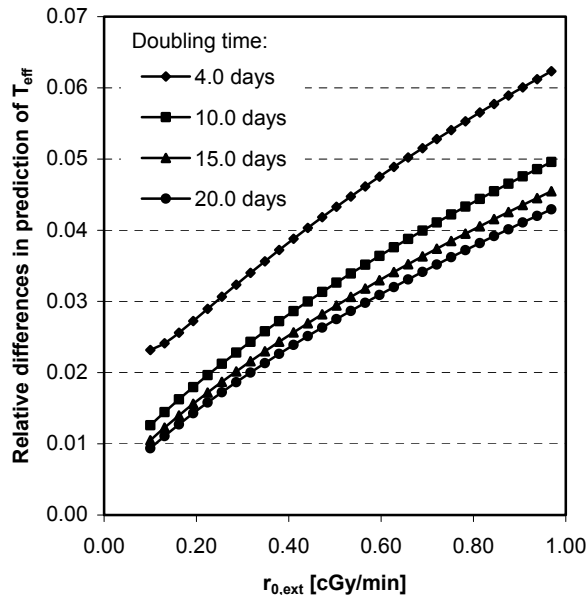
$$T_{eff}^{LQ} = \frac{1}{k_c} \ln \left[\frac{r_{0,ext}}{(\lambda/\alpha)} \right] \quad (11)$$

Substituting (11) in the equations (10.1)-(10.5) we could obtain equations similar to (7.2) and (8) to calculate the effective dose and the therapeutic efficacy when LQ model is used. In this condition,

from (11) we could obtain that $r_{crit}^{LQ} = \lambda/\alpha$. The figure

4a shows the relative differences in the values of T_{eff} predicted with both methods. The T_{eff} will decrease for rapid growing tumor and it will increased as effective elimination time will larger.

(a)



(b)

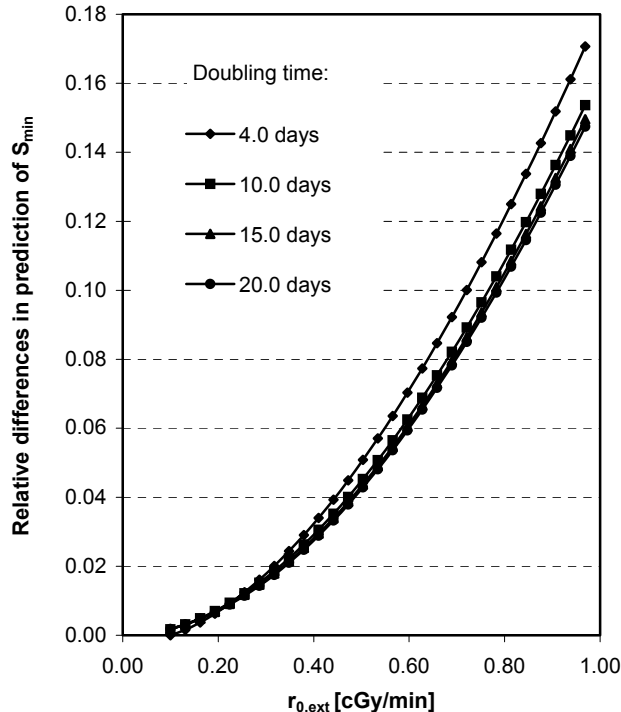


Figure 4. Relative differences in the prediction of the effective irradiation time done with Sanchez-Reyes and LQ radiobiological models adapted to be used in radionuclide therapy and considering the contribution of cell proliferation. **Parameters:** $T_u=1.0$ day, $T_e=5.0$ days, $r_{0,ext}=0.5$ cGy/min, $T_\mu=1.5$ hours, $\alpha/\beta=10$ Gy, $\alpha=0.35$ Gy $^{-1}$

However, the relative differences in T_{eff} predicted by both methods are small (around a day) and it depend mainly of α/β ratio, but it was not depended on effective elimination time of activity from tumor (data not shown). The figure 4b shows the relative differences in the response S_{min} predicted using both methods. It will increase as dose rate and the α/β ratio are increased below to 10% for dose rate less than 0.6cGy/min

Discussion

Saturable repair model can explain the radiobiological shouldered dose-response as alternative mechanistic explanation to the sublethal damage concept. These model can also produce ready explanations for several phenomena which are not readily explainable by other biophysical model [9,10]. There is yet a debate about where the curves will represent a saturable behaviour in cell repair mechanisms or its faults during the cell repair processes like sublethal model had been stated. In many works had been declared that in case of treatment with fractioning dose schemes the good response observed are because of the effects of saturation in the mechanisms repair as dose rate will be increased. However it is possible to obtain similar results in prediction with LQ model and saturable repair model for low dose rate [15].

For LQ model the parameters α and β will represent the contribution to effect by cells which die because of lethal damage (parameter α) and by interaction between sublethal damage or binary misrepair (parameter β). When irradiation is made continuously at low dose rate a modification to quadratic terms must be done by Lea-Catcheside factor decreasing the relative effectiveness RE, because part of damage will be repaired during irradiation [16]. When the contribution of cell proliferation is considered will appear a term λ/α that represent the lost in effectiveness per time unity of the dose rate due to cell growth which was defined by González et al [14] as relative therapeutic efficacy that represent the lost in RE when cell growth will influence in the response.

As it is discussed in [12] the biological signification of parameter α is the probability that cell dies when the repair mechanism remains intact and parameter β is the first interaction between repair mechanism and its destruction process caused by the dose. A similar representation to LQ was obtained here when the formulation of the Sánchez-Reyes model was adapted to be used in radionuclide therapy. The TE could be evaluated in order to know the effective fraction of total dose delivered and let us to predict the goal of the treatment as function of radiobiological and biokinetics parameters. This result will be important for treatment planning to obtain the better response and diminishing the undesirable side effect risk. On the other hand, the formulation will give us

the possibility for determining the irradiation condition for isoeffective treatments respect to a reference one, like brachytherapy or others, as well as, different radiopharmaceuticals are being used. The isoeffect will correspond to a horizontal straight line in figure 3. We can determine the adequate initial dose rate depending of the uptake and elimination times that produce biologically isoeffective responses that may be used in radionuclide therapy for treatment planning. O'Donoghue et al [4] had reported a similar description, but they not considering the contribution of the quadratic term arguing that it is not important at low dose rate. However, it could be noted that our description contains the former making $\beta \rightarrow 0$ in equation (4.1), but there are many evidences that quadratic term must be considered too [13,15,16].

When you evaluate the total effect and the biological effectiveness of irradiation keeping into account the repair and proliferation contribution the prediction of irradiation response with both model will produce similar results like appeared in figure 4a and 4b. The relative differences in the effective irradiation time T_{eff} and the effect given by S_{min} will be highly dependents on cell growth rate and a lesser way on biokinetics parameters effective uptake and elimination times. The relative differences will be less than 10% until dose rates around 6cGy/min, which is de dose rate interval reported to be important in radionuclide therapy nowadays for systemic application. However, new radiopharmaceutical like MAb fragments, synthetic peptides and others with higher affinities and better biokinetics behavior will improve these results.

Conclusions

The modification of radiobiological model proposed by Sanchez-Reyes presented here let us make prediction on cell response under irradiation schemes in radionuclide therapy. The model will produce similar result to those one which could be obtained with LQ model at low dose rate. The formalism could be used in the determination of parameters useful in the treatment planning in radionuclide therapy.

Resumen

El presente trabajo muestra un modelo de dosis-respuesta que permitiría hacer predicciones sobre la respuesta celular a la irradiación en condiciones de la terapia con radionúclidos a partir de una adaptación del modelo radiobiológico propuesto por Sánchez-Reyes [Radiact. Res., 1992;130:139-147] el cual considera que los mecanismos de reparación celular son saturables y pueden ser afectados por la acción de las radiaciones. Se considera que la tasa de dosis está distribuida uniformemente en todo el volumen tumoral y decae exponencialmente en función del tiempo. Se considera que la población celular tiene un crecimiento exponencial. Se obtuvieron expresiones analíticas para calcular el tiempo

efectivo de irradiación (T_{eff}), la dosis efectiva (D_{eff}) y la eficacia terapéutica (TE). Los resultados se compararon con las predicciones obtenidas para bajas tasas de dosis con el modelo lineal-cuadrático (LQ) considerando el factor de Lea-Catcheside en el término cuadrático en el modelo LQ de acuerdo a que los modelos de reparación saturable producen resultados similares a otros modelos que ofrecen una interpretación para el modelo LQ. El modelo propuesto produce resultados similares al modelo LQ par bajas tasas de dosis. La formulación presentada permite determinar parámetros que pueden utilizarse en la predicción de la respuesta a la irradiación en la radioterapia con.

Palabras clave: modelos dosis-respuesta; terapia con radionúclidos; bajas tasas de dosis; modelos de reparación saturable



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